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H_0 AND RELATED INDICATOR ACIDITY FUNCTIONS[1]

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I. INTRODUCTION

The H_0 acidity function is a quantitative measure of acidity conceived originally by Hammett and Deyrup (46). It is derived from ionization equilibria of a particular class of indicators, those behaving in the Brønsted–Lowry sense as uncharged bases,

$$B + H^+ \rightleftharpoons BH^+$$

and is defined (43, 44, 46) by the equation:

$$H_0 \equiv pK_{BH^+} - \log \frac{C_{BH^+}}{C_B} \tag{1}$$

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where C_{BH^+}/C_B is the directly observable concentration ratio of the indicator in its two differently colored forms and K_{BH^+} is the thermodynamic ionization constant of its conjugate acid in terms of molar concentrations, referred to ideal dilute solution in water. Analogous acidity functions derived from ionization equilibria of cationic and anionic bases may be defined as follows (44):

$$B^+ + H^+ \rightleftharpoons BH^{++}; \quad H_+ \equiv pK_{BH^{++}} - \log \frac{C_{BH^{++}}}{C_{B^+}} \tag{1a}$$

$$B^- + H^+ \rightleftharpoons BH; \quad H_- \equiv pK_{BH} - \log \frac{C_{BH}}{C_{B^-}} \tag{1b}$$

etc.

The above definitions are formally equivalent to:

$$H_0 = -\log \frac{a_{H^+} f_B}{f_{BH^+}} \tag{2}$$

$$H_+ = -\log \frac{a_{H^+} f_{B^+}}{f_{BH^{++}}} \tag{2a}$$

$$H_- = -\log \frac{a_{H^+} f_{B^-}}{f_{BH}} \tag{2b}$$

etc., where a_{H^+} denotes hydrogen-ion activity and the f's denote molar-concentration activity coefficients. A convenient function related to H_0 is h_0, defined by the equation $H_0 \equiv -\log h_0$; analogous functions h_+ and h_- may be defined for the other acidities.

The ionic activity and activity coefficient factors in equations 2 enter in the form of ratios or products that are observable in the sense described by Guggenheim (36). If each individual activity coefficient is taken by convention to approach unity at infinite dilution in water so that a_{H^+} under this condition becomes equal to C_{H^+},[2] then each of these acidity functions becomes equal to pH in ideal dilute aqueous solutions. With increasing acid concentration, however, and particularly with transfer to a nonaqueous medium, the various indicator acidity functions deviate from one another and also of course from other measures of acidity. No simple theory exists for calculation of the extent to which various ionic and nonionic solutes will depart from ideal dilute behavior at high electrolyte concentrations, particularly in media of low dielectric constant. Nevertheless we can certainly measure indicator concentration ratios directly and so apply equations such as 1, 1a, or 1b on an empirical basis.

Indicator procedures constitute only one of several possible ways to measure the acidity of solutions. A very simple method is to measure the concentration, C_A, of the acid itself; this is obviously of only limited utility for other than strong acids. Another measure is C_{H^+}, the concentration of hydrogen ion in the given solvent, but the determination and interpretation of this quantity are frequently uncertain. Furthermore, the value of C_{H^+} (or of C_A) is of little use in comparing acidities in different solvents. A different type of measurement is that of the potential of a hydrogen or equivalent electrode in equilibrium with the hydrogen ions of a solution. Such measurements outside the dilute aqueous range involve either a reference electrode with an indeterminate liquid-junction potential or, if a cell without a liquid junction is used, an interrelated contribution to the overall potential from the accompanying anions (3). As would be expected these different methods of measurement will usually lead to different values of the "acidity," and a point of major interest is to compare the values for different situations.

---

[2] The symbol H^+ is used, as is customary, to represent hydrogen ions in whatever equilibrium form they may assume in the given medium; e.g., presumably H_3O^+ in dilute aqueous solutions.

The indicator acidity functions themselves are differentiated from one another on the basis of charge type in recognition of the fact that to a first approximation, at least, this must be a major factor accounting for differences in behavior. Following the lead of Hammett and Deyrup, most investigators of indicator acidity in highly acid solutions have worked with H_0 rather than with other acidity functions. The generality of the H_0 function for aqueous solutions of strong acids has been established by the empirical observation that a series of different indicators of the given charge type, consisting in the main of aromatic amines and oxygen bases, has in fact been found to give a reasonably uniform scale of H_0 values independent of the particular indicator over acid concentrations extending far outside the ideal dilute range. Some degree of uniformity has been established also in certain nonaqueous media. By contrast, few systematic investigations have been reported on indicators of other charge types, and experimental evidence is not yet available as to whether functions such as H_+ or H_- are sufficiently independent of the indicator to be useful outside the dilute aqueous range.

The function H_0 serves specifically as a measure of the tendency for the solution in question to transfer a proton to an uncharged base molecule, increasingly negative values corresponding to higher acidity. The H_0 acidity scale has turned out to be useful for the measurement of base strength of very weak uncharged bases and also for the interpretation of the kinetics of certain classes of acid-catalyzed reactions. As a result there has been an increasing flow of information on various aspects of both this and related acidity functions (85a). The purpose of this review is to assemble the data on such functions and to evaluate their present status. Applications of the H_0 function to kinetic problems will be discussed in a subsequent review.

II. MEASUREMENT OF H_0

The measurement of H_0 falls into two phases, the measurement with a given indicator of C_{BH^+}/C_B and the measurement of pK_{BH^+}.

A. *Measurement of* C_{BH^+}/C_B

An indicator has an acid form and a base form (BH^+ and B, respectively, for the class of indicators here under consideration) with different spectral absorptions. All ordinary indicators show this difference in the visible part of the spectrum, but many other acids and bases which are transparent in the visible undergo a color change in the ultraviolet and hence can be used as indicators.

If ϵ_B^λ represents the extinction coefficient at a given wavelength of a solution containing the indicator practically completely in the basic form, B, and if $\epsilon_{BH^+}^\lambda$ represents the extinction coefficient of a solution in which the indicator is practically completely converted to the acid form, BH^+, then the ratio, C_{BH^+}/C_B, in a solution in which the indicator is partially ionized may be derived from its extinction coefficient, ϵ^λ, at the same wavelength by the equation,

$$\frac{C_{BH^+}}{C_B} = \frac{\epsilon_B^\lambda - \epsilon^\lambda}{\epsilon^\lambda - \epsilon_{BH^+}^\lambda} \qquad (3)$$

provided that the concentrations are sufficiently low so that the Beer–Lambert law is applicable and provided of course that one takes into account absorption by the medium itself. Since ϵ_B^λ and $\epsilon_{BH^+}^\lambda$ are necessarily measured in solutions of different composition from the test solution, one must be on guard against a possible shift in spectral absorption by the indicator accompanying changes in the medium not related to its acidity. Hammett and Deyrup noted such shifts with certain indicators in sulfuric acid–water solutions as the concentration of the acid was changed (46). One may minimize these so-called medium effects by taking ϵ_B^λ and $\epsilon_{BH^+}^\lambda$ values in solutions as close as possible to the range of acid concentrations over which significant change in the ionization ratio is actually taking place. Flexser, Hammett, and Dingwall (28) have given a detailed analysis of the problems involved, and Gold and Hawes (32) have discussed further aspects.

Most of the older data on indicators were obtained with optical colorimeters. More recent measurements have been made with photoelectric spectrophotometers. Aside from opening the ultraviolet region to convenient investigation, the spectrophotometer has afforded greater objectivity and precision in the measurements; it is furthermore inherently a more satisfactory instrument in that comparisons may be made under essentially monochromatic conditions in the most favorable part of the spectrum.

Until very recently all the published H_0 data were at room temperature, i.e., within about five degrees of 25°C. An explicit study of the temperature effect is now available for aqueous solutions of sulfuric, hydrochloric, and phosphoric acids (29a). This indicates a small but systematic shift in the relationships between H_0 and acid concentration with changing temperature. In the case of sulfuric acid, for example, the slope of $-H_0$ vs. molar concentration between 1 and 14 M averages about 5 per cent less at 80°C. than at 20°C.; the difference is somewhat greater if the solutions are compared on a weight composition basis, without correction for volume expansion. Even though the change of H_0 itself may be small, it is still highly desirable to control the temperature within a degree or so during precise indicator measurements, since both log C_{BH^+}/C_B and pK_{BH^+} vary separately to considerable extents. The value of pK_{BH^+} for *p*-nitroaniline, for example, is reported to change by -0.20 logarithmic unit between

20°C. and 40°C. Temperature fluctuations during the measurements can therefore certainly lead to errors in $C_{\mathrm{BH}^+}/C_{\mathrm{B}}$ values.

B. Measurement of pK_{BH^+}

The definition of $\mathrm{p}K_{\mathrm{BH}^+}$ is

$$\mathrm{p}K_{\mathrm{BH}^+} = \log \frac{C_{\mathrm{BH}^+}}{C_{\mathrm{B}}C_{\mathrm{H}^+}} + \log \frac{f_{\mathrm{BH}^+}}{f_{\mathrm{B}}f_{\mathrm{H}^+}} \tag{4}$$

where the activity coefficients are referred to the value unity for an infinitely dilute solution in water. Noting that the indicator concentration is always exceedingly small, this is equivalent to

$$\mathrm{p}K_{\mathrm{BH}^+} = \lim_{C_{\mathrm{A}}\to 0} \left[\log\left(\frac{C_{\mathrm{BH}^+}}{C_{\mathrm{B}}}\right) - \log C_{\mathrm{H}^+}\right] \tag{5}$$

where C_{A} is the molar concentration of a strong acid, A, in water. For a strong acid, C_{H^+} is calculable by the relation $C_{\mathrm{A}} = C_{\mathrm{H}^+} + C_{\mathrm{BH}^+}$, assuming that the indicator is introduced in its uncharged form. Hence for an indicator base whose ionization ratio can be directly measured in dilute aqueous solutions of strong acids, one can expect to calculate $\mathrm{p}K_{\mathrm{BH}^+}$ from the observed values of C_{A} and the indicator ratio. Empirical evidence shows that the expression in brackets on the righthand side of equation 5, which is equivalent to $\mathrm{p}K_{\mathrm{BH}^+} + \log (f_{\mathrm{H}^+}f_{\mathrm{B}}/f_{\mathrm{BH}^+})$, varies linearly with concentration of electrolyte up to at least 2 *M* concentration (77). Apparently the general effects of interionic attraction on the ionic activity coefficients in equation 4 approximately cancel out over this range. The extrapolation procedure is therefore quite precise for sufficiently strong indicator bases (see figures 2 and 3).

For weaker bases this type of direct determination of $\mathrm{p}K_{\mathrm{BH}^+}$ is not feasible and a stepwise comparison must be used. With two different indicator bases, B and C, which are studied in the same solution,

$$\mathrm{p}K_{\mathrm{CH}^+} - \mathrm{p}K_{\mathrm{BH}^+} = \log\left(\frac{C_{\mathrm{CH}^+}}{C_{\mathrm{C}}}\right) - \log\left(\frac{C_{\mathrm{BH}^+}}{C_{\mathrm{B}}}\right) - \log\left(\frac{f_{\mathrm{C}}f_{\mathrm{BH}^+}}{f_{\mathrm{CH}^+}f_{\mathrm{B}}}\right) \tag{6}$$

If the bases B and C are of fairly similar structure, there are, as Hammett (44) points out, both experimental and theoretical reasons for believing that the last term on the right can be neglected for aqueous solutions and presumably for solutions in other solvents of high dielectric constant. Given that the bases B and C have ionization constants sufficiently close together so that both indicator ratios can be measured with good precision in the same medium, the differences in the p*K* values can be determined by the relation:

$$\mathrm{p}K_{\mathrm{CH}^+} - \mathrm{p}K_{\mathrm{BH}^+} = \log\left(\frac{C_{\mathrm{CH}^+}}{C_{\mathrm{C}}}\right) - \log\left(\frac{C_{\mathrm{BH}^+}}{C_{\mathrm{B}}}\right) \tag{7}$$

A similar procedure will give $\mathrm{p}K_{\mathrm{DH}^+} - \mathrm{p}K_{\mathrm{CH}^+}$ for an indicator D whose ionization overlaps that of C and so on. The absolute values of all the p*K*'s can then

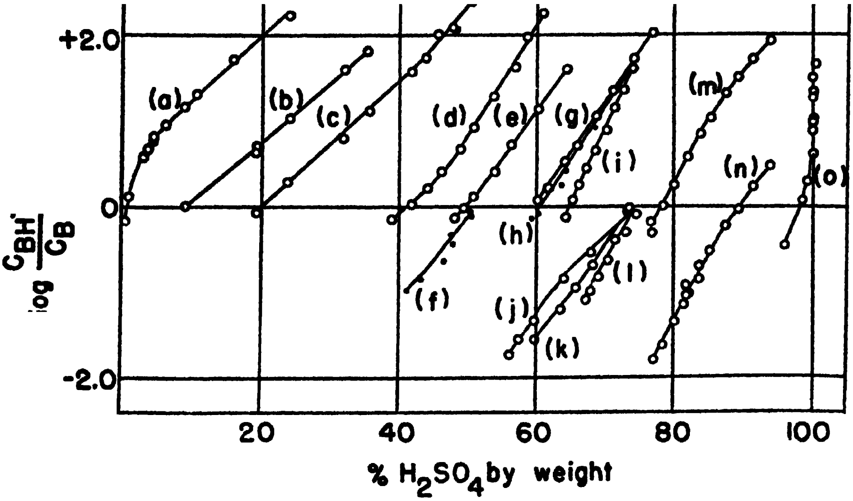

FIG. 1. Logarithm of ionization ratios of indicators in sulfuric acid–water solutions. Indicators: (a) *p*-nitroaniline; (b) *o*-nitroaniline; (c) 4-chloro-2-nitroaniline; (d) *p*-nitrodiphenylamine; (e) 2,4-dichloro-6-nitroaniline; (f) *p*-nitroazobenzene; (g) 2,6-dinitro-4-methylaniline; (h) 2,4-dinitroaniline; (i) *N*,*N*-dimethyl-2,4,6-trinitroaniline; (j) benzalacetophenone; (k) β-benzoylnaphthalene; (l) *p* benzoylbiphenyl; (m) 6-bromo-2,4-dinitroaniline; (n) anthraquinone; (o) 2,4,6-trinitroaniline (46).

be established if any one of them is determined by direct measurement in dilute aqueous solution.

There are two obvious experimental tests of equation 7 and hence of the validity of this stepwise procedure. One is to see if $\left[\log\left(\frac{C_{CH^+}}{C_C}\right) - \log\left(\frac{C_{BH^+}}{C_B}\right)\right]$ remains constant as the concentration of a particular strong acid in a given solvent is varied. The second test is to see if the value of this difference, and hence of $pK_{CH^+} - pK_{BH^+}$, remains constant in different solvents. Figure 1 is an illustration of the first type of test, taken from the studies of Hammett and Deyrup on aqueous sulfuric acid. It is evident that the plots of $\log C_{BH^+}/C_B$ remain parallel for almost all the indicators studied.

The indicator *p*-nitroaniline, (a) of figure 1, is a sufficiently strong base that its p*K* value can be directly measured by application of equation 5. Sulfuric acid solutions themselves are not suitable for this purpose because of complications in the establishment of C_{H^+} arising from secondary ionization. The strong acids perchloric, hydrochloric, and nitric may, however, be used. Figure 2 gives plots of $\left[\log \frac{C_{BH^+}}{C_B} - \log C_{H^+}\right]$ vs. C_A from spectrophotometric measurements for *p*-nitroaniline in aqueous solutions of hydrochloric acid. The data of Paul (77) extrapolate to a p*K* value of 0.99 for this indicator; those of Braude (14) extrapolate to 0.98[3]; older colorimetric data (51) (not shown on the figure)

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[3] The authors are unable to account for the difference in slope between the data of Braude and those of Paul (figure 2). Braude introduces two modifications into the procedure for

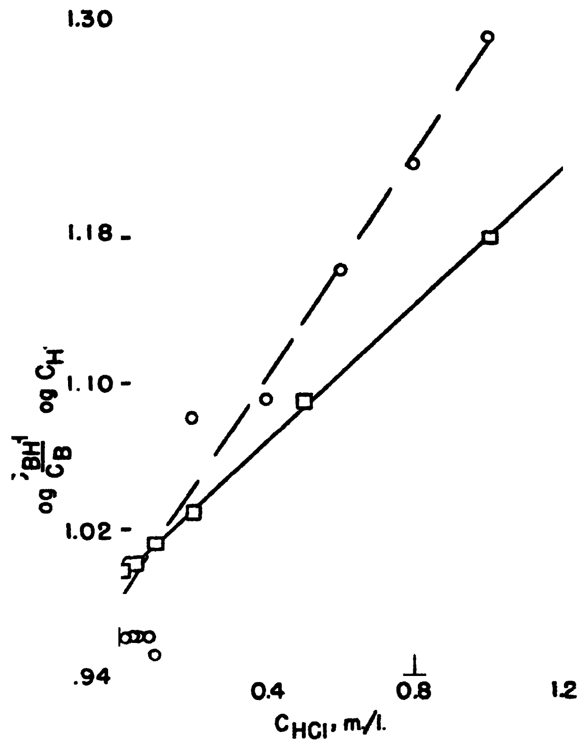

FIG. 2. Plot for determination of pK_{BH^+} for *p*-nitroaniline in aqueous hydrochloric acid. ○, Braude (14); □, Paul (77).

extrapolate to 1.03. Bell and Bascombe (6) give a value of 1.01 from measurements in approximately 0.01 *M* hydrochloric acid; Hart (54) has very recently obtained the value 0.98 ± 0.005.

Figure 3 shows a similar plot for aqueous solutions of perchloric acid from colorimetric data (46). Included also are data for the weaker bases *o*-nitroaniline and 4-chloro-2-nitroaniline (46), and it is of interest to note that the curves are accurately parallel even though they are no longer linear at the higher acidities. The data of figure 3 for *p*-nitroaniline extrapolate to 0.47; data obtained

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determining the indicator ratio. He takes explicit account of a small optical absorption by the *p*-nitroaniline ion and this seems to be quite reasonable. He also assumes that the wavelength of maximum absorption for the uncharged base shifts with electrolyte concentration and consequently determines C_{BH^+}/C_B from readings at shifting wavelength. This latter procedure may be responsible for the large discrepancy between Braude's H_0 values and those of other investigators for 2 and 3 *M* hydrochloric acid, but it should not significantly influence the data of figure 2. Braude's proposed value of 0.95 for the pK_{BH^+} of *p*-nitroaniline is based exclusively on the observed ionization ratio at hydrochloric acid concentrations of 0.1 *M* and below, on the assumption that in these solutions the activity coefficient ratio in equation 4 is practically equal to unity. The extrapolation procedure suggested in figure 2 seems sounder in principle. See, for example, figure 4 of reference 4, where a similar extrapolation procedure is used.

in nitric acid solutions (51) extrapolate to 1.03. $pK_{BH^+} = 0.99$ is selected as a best value for *p*-nitroaniline. This value is 0.12 unit more negative than the value of 1.11 previously adopted on a somewhat different basis by Hammett and Paul (51), and 0.41 unit more negative than that of 1.40 originally adopted by Hammett and Deyrup.

Table 1 gives pK_{BH^+} values for a series of uncharged basic indicators in various acid media. Those above *p*-naphtholbenzein (stronger bases) were determined by direct extrapolation as in figures 2 and 3. The others were determined by stepwise comparison, with *p*-nitroaniline as the ultimate reference base. For many of these, cryoscopic studies in 100 per cent sulfuric acid have definitely established that they ionize by adding a single proton (48). One will observe that there is general, if not perfect, agreement among the pK_{BH^+} values obtained in the different media, including the nonaqueous ones, thus providing a

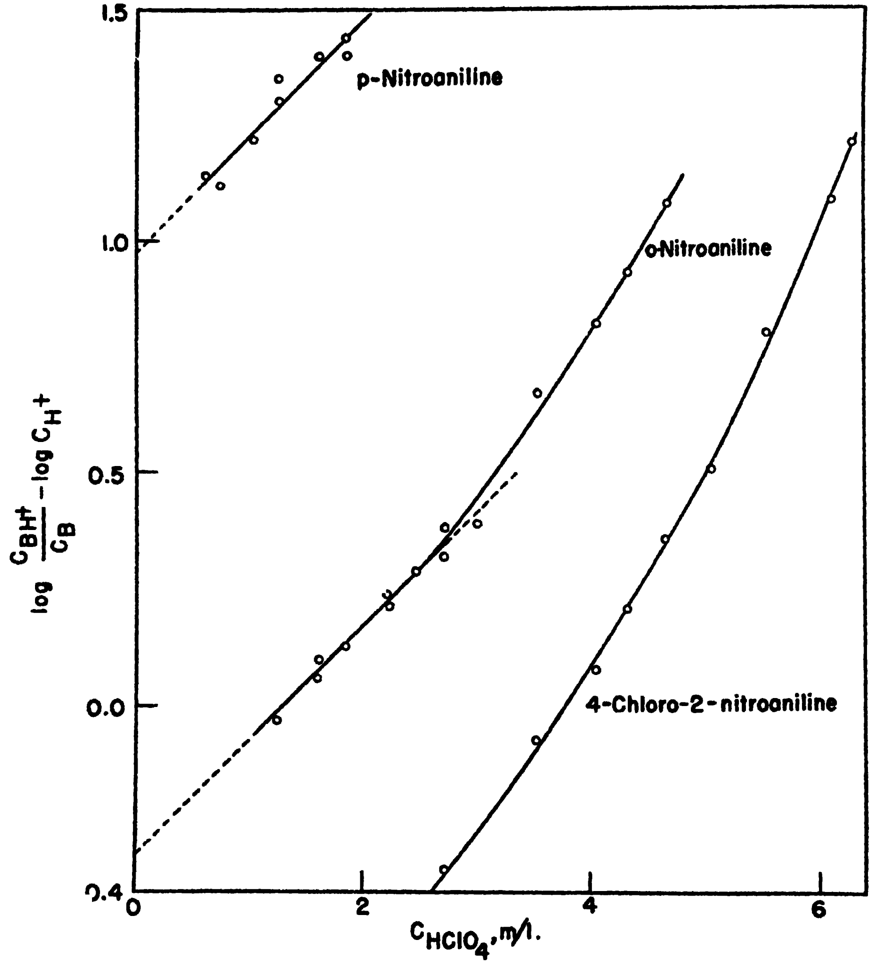

FIG. 3. Ionization of indicators in aqueous perchloric acid (46)

TABLE 1

Indicator constants, pK_{BH^+}, *of very weak bases*

Indicator	Best Value	HCl aq.	HNO_3 aq. (51)	H_2SO_4 aq. (46)	$HClO_4$ aq. (46)	H_3PO_4 aq. (55)	HF aq. (7)	$C_6H_5SO_3H$ in HCOOH (47)	H_2SO_4 in CH_3COOH
By direct extrapolation(a)									
p-Aminoazobenzene	2.77	2.76 (51) 2.78 (6)			2.78 (6)				
m-Nitroaniline	2.50	2.43 (16)(b) 2.50 (6) 2.57 (4)							
2,4-Dichloroaniline	2.00	2.00 (77)							
Benzeneazodiphenylamine	1.42	1.42 (51)							
p-Nitroaniline	0.99	1.03 (51) 0.99 (77) 1.01 (6) 0.98 (54) 0.95(c)	1.03		0.97				
Diphenylamine	0.78	0 78 (77)							
By stepwise comparison (with ultimate reference to *p*-nitroaniline, $pK_{BH^+} = 0.99$)									
p-Naphtholbenzein	0 41(d)								
2,4-Dinitro-*N*,*N*-diethylaniline	0 18(e)								
2,6-Dichloro-4-nitro-*N* *N* dimethylaniline	−0.23(e)								
o-Nitroaniline(f)	−0.29	−0.29 (51)	−0.32	−0.25	−0.31	−0.22	−0.27		
4-Chloro 2 nitroaniline(g)	−1 03	−1 03 (51)	−1.09	−0.97	−1.03	−1.01	−1.03	−1.06	−1.03 (78)
4-Chloro 2-nitro-*N* methylaniline	−1 49(e)								
p-Nitrodiphenylamine	−2 48	−2.47 (9		−2.50		−2.26		−2 63	
2,4-Dichloro-6-nitroaniline	−3 32			−3.34	−3.30	−3.10		−3.43	−3.79 (41)
p-Nitroazobenzene	−3 47			−3 47	−3.47			−3.41	
2,6-Dinitro-4-methylaniline	−4 44			−4.44					−4.57 (41)
2,4-Dinitroaniline	−4 53			−4.50	−4.55				
N,*N*-Dimethyl-2,4,6-trinitroaniline(h)	−4 81			−4.81					−4.85 (41)
Benzalacetophenone(h)	−5 73			−5.73					
β-Benzoylnaphthalene	−6.04			−6.04					
p-Benzoylbiphenyl	−6 31			−6.31					
6-Bromo 2,4-dinitroaniline	−6.71			−6.71					
Anthraquinone	−8.27			−8.27					
2,4,6 Trinitroaniline	−9.41			−9.41					
p Nitrotoluene	−10 46			−10.46 (10, 12)					
Nitrobenzene(i)	−11.38			−11.38 (10)					
2,4 Dinitrotoluene	−12.78			−12 78 (12)					

(a) By the method indicated in figures 2 and 3 from data published in the references cited.

(b) Given as 2.52 in reference 98

(c) Reference 14, as given by the author; see, however, figure 2

(d) Determined with perchloric acid in glacial acetic acid (93).

(e) Determined with perchloric acid in glacial acetic acid (61).

(f) $pK_{BH^+} = -0.36$ in trichloroacetic acid-water and -0.25 in trifluoroacetic acid–water (83).

(g) $pK_{BH^+} = -1.06$ in trifluoroacetic acid-water (83).

(h) These are probably not satisfactory indicators, judging by the departure of their ionization curves from parallelism with those of other indicators (see figure 1). The indicator *N*,*N*-dimethyl-2,4,6-trinitroaniline shows similar eccentricity in solutions of sulfuric acid in anhydrous acetic acid (reference 41 and figure 10).

(i) pK_{BH^+} values for other substituted nitrobenzenes are given in reference 12.

satisfactory answer to the second form of test mentioned previously. It is noteworthy, for example, that pK_{BH^+} for *o*-nitroaniline given by a direct extrapolation of the perchloric acid data in figure 3 is in good agreement with the values given by stepwise comparison in the other media. The second column of table 1 gives "best" values for pK_{BH^+} based on all the available evidence. Since it is desirable that all H_0 values should be based on the same reference state, one of infinite dilution in water, these "best" pK_{BH^+} values should be used uniformly for all media.

C. *Justification and limitations of the H_0 acidity scale*

The two experimental tests discussed above for the validity of the determination of pK values are also direct justification of the concept of an H_0 acidity scale. The general parallelism of the plots of figures 1 and 3 strongly suggests that all the indicators are measuring the same property of the solutions, a property which is apparently not a function of the indicator used. This same conclusion is also indicated by application of a more explicit comparison of slopes for adjacent indicators in the manner proposed by Deno, Jaruzelski, and Schriesheim (23). The fact that studies with aqueous solutions of several different strong acids result in almost identical values of pK_{BH^+} for the various indicators (columns 3 to 6 of table 1) shows that the equality

$$\frac{f_B}{f_{BH^+}} = \frac{f_C}{f_{CH^+}}$$

holds for pairs of indicators in solutions of quite different character. These points lead to the conclusion that H_0 as defined in equation 2 is independent of the indicator used and in this sense appears to be a property only of the solution being measured.

The indicators of figure 1 and table 1 involve some marked variations in structure. They include amines, azo compounds, ketones, and quinones. At the same time they possess many points of similarity. They are of approximately the same molecular size and are all aromatic compounds. In fact, the large majority are nitroanilines. It is certainly possible and even probable that indicators of markedly different size or type, for example, an aliphatic amine, might not give the same results as does this group. Even within this limited group there are clear examples of individual behavior. Thus in figure 1 curves (i) and (j) are clearly not parallel to their neighbors. Use of the two indicators concerned, N,N-dimethyl-2,4,6-trinitroaniline and benzalacetophenone, could quite evidently lead to different values of H_0. One may safely predict that similar discrepancies will show up if studies are made of other indicators with widely different size or structure.

As another example of specific behavior, two of the pK_{BH^+} values obtained from studies with aqueous phosphoric acid differ by about 0.2 unit from the values obtained with other aqueous solutions (table 1). This type of behavior is very evident for solutions in nonaqueous and mixed solvents. It is difficult to escape the conclusion that an H_0 acidity function may be experimentally justifiable for one solvent but not for some other. For the particular case of aqueous solutions of strong acids, the data of the previous section constitute ample evidence that an adequately general H_0 function does exist. For other solvents, even aqueous solutions of weak acids, for example, the question of an H_0 function which is reasonably independent of the choice of indicator can only be answered by experiment.

III. VALUES OF H_0 FOR AQUEOUS SOLUTIONS

A. "Strong" acids

Most of the data on the acidity function for aqueous solutions of the more common strong acids go back to the original studies of Hammett, Deyrup, and Paul. These studies were made by colorimetric methods, using the indicators of figure 1. More recently, studies have been made of aqueous solutions of hydrochloric acid (9), of phosphoric acid (55, 81), and of hydrofluoric acid (7), again with some of the indicators of figure 1 but using spectrophotometric measurement of the indicator ratio. All these data have been replotted and tables of "best values" of the acidity function have been prepared. Two different ideas have guided the presentation of the data. One is the belief that, at least for not too concentrated solutions of the strong acids, the most useful concentration unit is moles per liter. The second is the belief that, since pK values are by definition constant (at a constant temperature) and independent of the medium, it is desirable to use a single, consistent set of pK values. Specifically, the "best values" given in table 1 have been used for all calculations of H_0. The result is that the H_0 values in the subsequent tables differ from those of previous tabulations by small but varying amounts. For example, with most of the indicators used for aqueous solutions of sulfuric acid the H_0 values of the authors are more negative than those of Hammett (44) by 0.12 unit. However, with *o*-nitroaniline they are more negative by 0.16 unit and with 4-chloro-2-nitroaniline they are more negative by 0.18 unit. Similar fluctuations enter for other solutions.

Data for aqueous solutions of six common acids are presented in table 2. When available, values of H_0 are given for concentrations of from 0.1 to 10 M. These data will permit construction of graphs for satisfactory interpolation to give intermediate values of H_0. It is difficult to assign meaningful estimates of error in table 2, but it is doubtful whether even relative values of H_0 should ever be considered as known to better than ±0.05 outside of the dilute aqueous range. In some cases the margin of error is considerably greater than this.

Figure 4 gives a plot of H_0 vs. molarity for these acids. The order of acid strength which this plot suggests is consistent with accepted notions. Thus perchloric acid is generally considered to be slightly the strongest of these, followed closely by sulfuric acid, and then by hydrochloric and nitric acids (52, 90). The other two acids, phosphoric and hydrofluoric, give distinctly less acid solutions as judged by the H_0 values. Since in dilute aqueous solution these two acids are known to be measurably weak [$pK_{H_3PO_4} = 1.85$ (80) and $pK_{HF} = 3.17$ (17)], this is the expected result. The molarity scale may be somewhat

TABLE 2

H_0 at selected molarities of aqueous solutions, 25°C.

Acid centration	Acid					
	HNO_3	HCl	$HClO_4$	H_2SO_4	H_3PO_4*	HF
les per liter						
0.1	+0.98	+0.98	—	+0.83	+1.45	—
0.25	+0.55	+0.55	—	+0.44	+1.15	—
0.5	+0.21	+0.20	—	+0.13	+0.97	—
0.75	−0.02	−0.03	−0.04	−0.07	+0.78	—
1.0	−0.18	−0.20	−0.22	−0.26	+0.63	+1.20
1.5	−0.45	−0.47	−0.53	−0.56	+0.41	+1.04
2.0	−0.67	−0.69	−0.78	−0.84	+0.24	+0.91
2.5	−0.85	−0.87	−1.01	−1.12	+0.07	+0.74
3.0	−1.02	−1.05	−1.23	−1.38	−0.08	+0.60
3.5	−1.17	−1.23	−1.47	−1.62	−0.22	+0.49
4.0	−1.32	−1.40	−1.72	−1.85	−0.37	+0.40
4.5	−1.46	−1.58	−1.97	−2.06	−0.53	+0.34
5.0	−1.57	−1.76	−2 23	−2.28	−0.69	+0.28
5.5	−1.69	−1.93	−2.52	−2.51	−0.84	+0.21
6.0	−1.79	−2.12	−2.84	−2.76	−1.04	+0.15
6 5	−1.89	−2.34	−3.22	−3.03	−1.24	+0.08
7.0	−1.99	−2.56	−3.61	−3.32	−1 45	+0.02
7.5		−2.78	−3.98	−3.60	−1 66	−0.04
8.0		−3.00	−4.33	−3.87	−1.85	−0.11
8.5		−3.21	−4.69	−4.14	−2.04	−0 17
9.0		−3.39	−5.05	−4.40	−2.22	−0.24
9.5		−3.54	−5.42	−4.65	−2.40	−0.30
10.0		−3.68	−5.79	−4.89	−2.59	−0.36

* Studies at 19°C.

Added in proof Values of H_0 have recently been reported for aqueous hydrobromic acid solutions (98a). All data were obtained spectrophotometrically at temperatures between 22°C. and 26°C. Corrected to the same reference basis as tables 1 and 2 the results at rounded molarities are as follows:

C_{HBr}	H_0	C_{HBr}	H_0	C_{HBr}	H_0
moles per liter		*moles per liter*		*moles per liter*	
0.1	0.98	3	−1.11	7	−2.85
0.5	0.20	4	−1.50	8	−3.34
1	−0.20	5	−1.93	9	−3 89
2	−0.71	6	−2.38	10	−4.44

In addition to the indicators of table 1 the investigators used 5-chloro-2-nitroaniline, for which they obtained $pK_{BH^+} = -1.32$ (corrected to the scale of table 1). They report measurements also for aqueous hydrochloric acid; H_0 values for the higher molarities are as follows:

C_{HCl}, moles per liter .	6	9	10	11	12	13
H_0..	−2.12	−3.22	−3.59	−3.99	−4.41	−4.82

These results show a slightly more consistent trend than those listed in table 2 (9).

misleading in the case of hydrofluoric acid, since this substance is supposed to be dimerized to a considerable extent at the higher concentrations (79).

H_0 values are available at higher concentrations than 10 M for hydrofluoric (7),[4] phosphoric (55), and sulfuric acids. Data for the latter are discussed in a later section.

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[4] Values for hydrofluoric acid covering the entire range of aqueous compositions have very recently been reported by Kilpatrick and Hyman (56a), using the aromatic hydro-

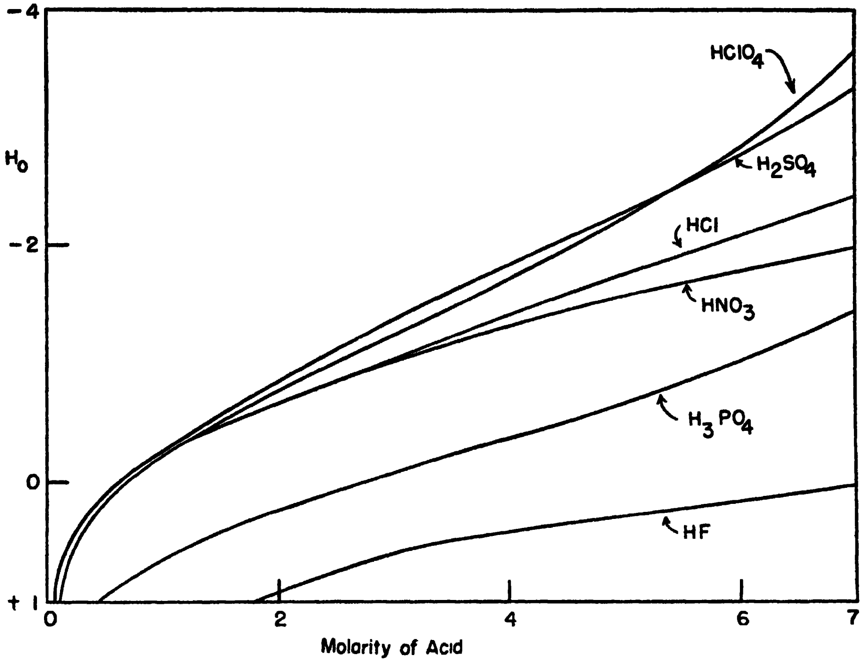

FIG. 4. H_0 for aqueous solutions of acids

For a typical strong monobasic acid such as perchloric, the distinctive feature of H_0 is the rapid increase of $-H_0$ as compared with log C_{H^+} (see figure 5). Although one can quite properly accept H_0 as a measured quantity on a purely empirical basis, it is still instructive to speculate about its detailed makeup. Writing H_0 as

$$-H_0 = \log C_{H^+} + \log f_{H^+}/f_{BH^+} + \log f_B \tag{8}$$

one can ask about the relative importance of the three terms on the righthand side of equation 8. From figure 5 it is apparent that at high molarities log C_{H^+} accounts for only a modest fraction of the total magnitude of $-H_0$. The last term, log f_B, represents the salt effect of the strong acid on the neutral base, B. From general studies of salt effects on nonelectrolytes (64) it is reasonable to conclude that the acids hydrochloric, nitric, sulfuric, and perchloric have little general tendency either to salt in or salt out. One may tentatively conclude that for these acids the term log f_B makes only a small contribution to H_0. Thus a large part of the departure of $-H_0$ from log C_{H^+} must be due to the term log $_{H^+}/f_{BH^+}$. It is at least plausible that this term is large and positive at high acid concentrations, since various studies suggest that the influence of electrolyte concentration on the activity coefficient of a small cation can become very large relative to that on a large cation.

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carbons benzene, mesitylene, and hexamethylbenzene as indicators. The value of H_0 for the anhydrous acid is -9.9.

It is also instructive to note in figure 5 that for perchloric acid the acidity as measured by H_0 increases considerably faster than does log $a_{\pm}$, where $a_{\pm}$ is the mean ionic activity (85). This is not surprising, since log $a_{\pm}$ measures the average escaping tendency of both ions, whereas $-H_0$ is more nearly a measure of the escaping tendency of hydrogen ions only.

Kuivila (60) has recently reported that for aqueous solutions of the three acids phosphoric, perchloric, and hydrochloric (but not for sulfuric), there is a linear correlation between $-H_0$ and log (a_{HX}/a_{H_2O}) of the form:

$$-H_0 = \alpha + \beta \log \frac{a_{HX}}{a_{H_2O}}$$

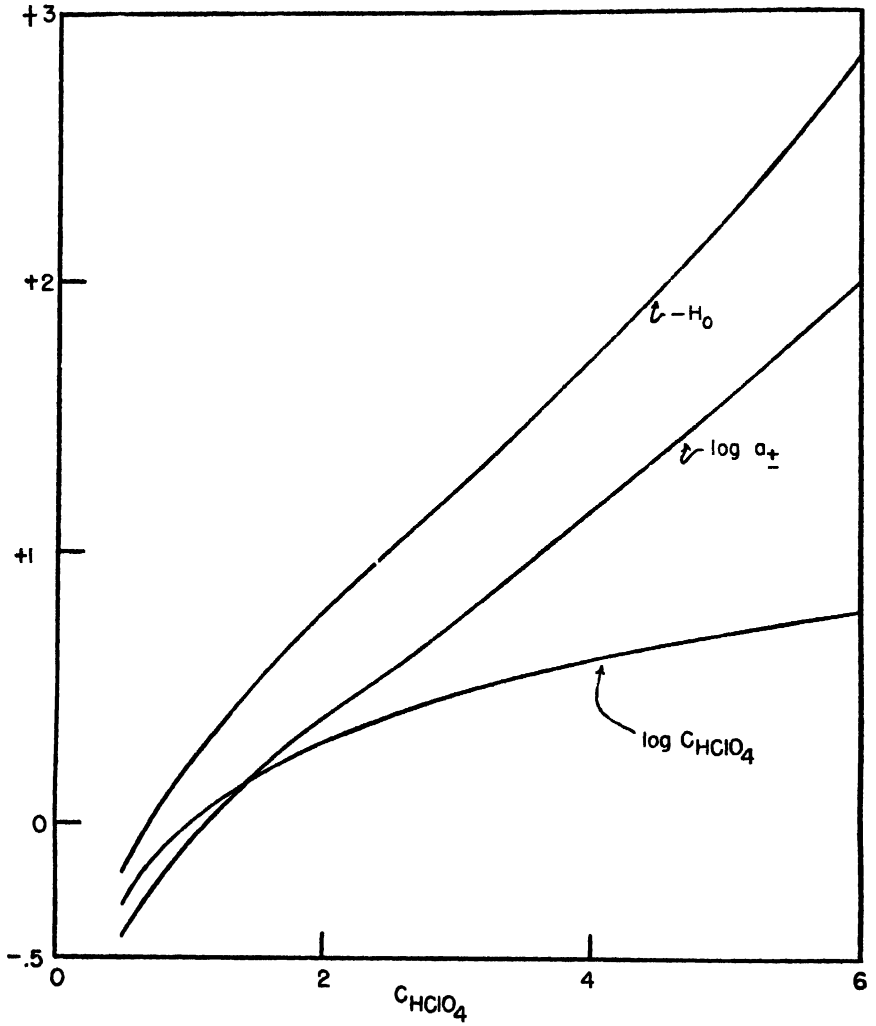

FIG. 5. Comparison of $-H_0$ (46) and log $a_{\pm}$ (85) with log C for aqueous perchloric acid

TABLE 3

H_0 for selected percentages of sulfuric acid in water, 25°C.

H_2SO_4	$-H_0$	H_2SO_4	$-H_0$	H_2SO_4	SO_3	$-H_0$
per cent		*per cent*		*per cent*	*per cent*	
10	0.31	80	6.97	100.0	0.00	11.10
15	0.66	85	7.66	100.1	0.44	11.30
20	1.01	90	8.27	100.2	0.89	11.43
25	1.37	95	8.86	100.3	1.33	11.52
30	1.72	96	8.98	100.5	2.22	11.66
35	2.06	97	9.14	100.7	3.11	11.75
40	2.41	98	9.36	101.0	4.44	11.82
45	2.85	99	9.74	101.5	6.66	11.95
50	3.38	99.3	9.89	102.0	8.9	12 06
55	3.91	99.5	10.03	102.5	11.1	12.18
60	4.46	99.7	10.22	103	13.3	12.28
65	5.04	99.8	10.36	104	17.8	12.47
70	5.65	99.9	10.59	105	22.2	12.62
75	6.30	100.0	11.10	106	26.6	12.74
				107	31.1	12.87

Actually, Kuivila made his calculations with a_{HX}, the activity of the solute, only for the case of phosphoric acid, and in this case the data refer specifically to the activity of the undissociated species. With the other three acids the quantity used for a_{HX} was in fact $m\gamma_{\pm}$, which for hydrochloric and perchloric acids is $a_{\pm}$ or $\sqrt{a_{HX}}$ and which for sulfuric acid is $(a_{H_2SO_4}/4)^{1/3}$. In view of these complications it is difficult to ascribe any general significance to the reported correlations.

A quite different sort of correlation with H_0 was noted by Michaelis and Granick (72), who showed that a measurement of the E.M.F. of certain cells involving dyestuffs in aqueous sulfuric acid gave an acidity scale which was reasonably parallel to H_0. The systems are quite complex and no interpretation of the correlation was attempted.

B. Concentrated solutions of sulfuric acid

Values of H_0 were determined by Hammett and Deyrup for water–sulfuric acid mixtures up to and including anhydrous sulfuric acid. These data have recently been extended to "oleum" solutions of as high as 107 per cent sulfuric acid, i.e., 32 weight per cent sulfur trioxide in anhydrous sulfuric acid (10, 12). Figure 6 gives a plot of the sulfuric acid data for the complete concentration range. Table 3 gives selected H_0 values for solutions containing 10 per cent or more of sulfuric acid, with emphasis on solutions of from 99 to 107 per cent sulfuric acid. These latter data are of considerable interest, both because of the very high acidity and because of the continuous nature of the function in going from solutions of water in sulfuric acid to those of sulfur trioxide in sulfuric acid.

Data are also available for the acidity of solutions of potassium sulfate and of barium di(methylsulfate) in various oleum solutions (10). As expected, these salts decrease the acidity of the oleum mixtures.

Lewis and Bigeleisen (62) have reported H_0 data for solutions of sulfur trioxide

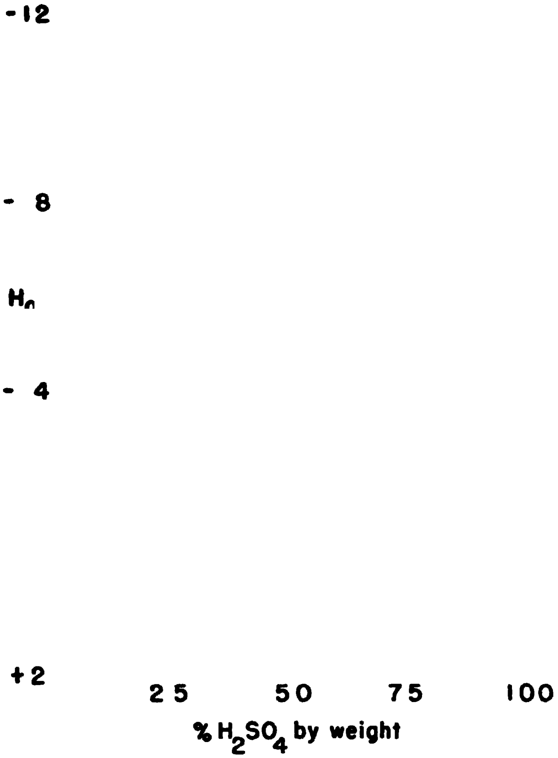

FIG. 6. H_0 for mixtures of sulfuric acid with water and with sulfur trioxide (12, 46)

in anhydrous sulfuric acid. However, the indicator used is not an uncharged base, so it is perhaps not surprising that agreement with the data of Brand is poor. No weight has been given either to the Lewis and Bigeleisen values of H_0 or to the interpolated values of them as tabulated by Coryell and Fix (18). One of the proposals of these investigators (18, 62) is that for fuming sulfuric acid, the value of $-H_0$ increases at the same rate as log p_{SO_3}, where p_{SO_3} is the vapor pressure of sulfur trioxide in the oleum. Actually, a comparison of Brand's $-H_0$ data with values of log p_{SO_3} (13) shows that the proposed parallel behavior does not occur; log p_{SO_3} (at 50°C.) for the range 4 to 30 per cent sulfur trioxide increases distinctly more rapidly than does $-H_0$. This is not really surprising, since there is no particular reason to expect the indicator acidity to be determined solely by the activity of the sulfur trioxide.

Deane (20) has suggested that the value of H_0 for fuming sulfuric acid could be obtained from kinetic data for the decomposition of *o*-benzoylbenzoic acid in this medium. In view of the existence of Brand's indicator studies, this suggestion has not been followed.

The indicator acidity function increases quite smoothly for increasing concentrations of sulfuric acid. Even so, it must be noted that the absolute values of H_0 cannot be considered to be very firmly established beyond about 75 per cent sulfuric acid. The reason is that beyond this there are two places where the overlap in the ranges of the indicators is so poor as to make the pK value of the weaker base somewhat doubtful. As figure 1 shows, a poor overlap occurs between indicators (g) [or (l)] and (m) and again between indicators (n) and (o). It will be very desirable to discover some additional indicators for these acidity regions and use them to establish the acidity scale more certainly.

Brand (10) and also Deno and Taft (25) have attempted to account for the change of H_0 with acid concentration in the region just below 100 per cent sulfuric acid in terms of the ionization reaction:

$$H_2SO_4 + H_2O = H_3O^+ + HSO_4^-$$

The equimolar H_2SO_4:H_2O composition corresponds to 84.5 per cent acid. Brand showed that between 90 and 99.8 per cent acid, H_0 satisfies closely the relationship:

$$H_0 = -8.48 + \log \frac{x_{HSO_4^-}}{x_{H_2SO_4}}$$

where the mole fractions, $x_{HSO_4^-}$ and $x_{H_2SO_4}$, are computed on the basis that the ionization reaction goes to completion (the constant term has been adjusted to the present H_0 scale by addition of −0.12 to the published value). Deno and Taft found that the range of the relationship could be extended down to 83 per cent acid by assuming for the ionization reaction an equilibrium constant of 50. The relationship of H_0 to the water concentration then assumes the form

$$H_0 = -6.78 + \log \frac{x}{x_{H_3O^+}}$$

Deno and Taft interpret these results on the basis that the activity coefficients involved approach constancy in 83–99.8 per cent sulfuric acid solutions.

Solutions of chlorosulfonic acid in anhydrous sulfuric acid have also recently been investigated with the indicators *p*-nitrochlorobenzene and 2,4-dinitrotoluene (76b). The value of H_0 decreases steadily with increasing chlorosulfonic acid concentration, 100 per cent HSO_3Cl being more acid than 100 per cent H_2SO_4 by 1.89 logarithmic units. The value obtained for pK_{BH^+} of *p*-nitrochlorobenzene is −11.70 based on $H_0 = -11.10$ for 100 per cent H_2SO_4 (table 3), while the value for 2,4-dinitrotoluene corrected to the same basis is −12.95; this compares with −12.78 (table 1) derived from measurements with solutions of sulfur trioxide in anhydrous sulfuric acid (12).

C. *Effect of neutral salts on H_0*

Only a few systematic studies have been reported on the influence of added salts on the acidity function; the results are of considerable interest. Harbottle (53) studied a set of perchloric acid–sodium perchlorate solutions all at a total electrolyte concentration of 6 *M*. Table 4 gives the data corrected to the pK_{BH^+}

TABLE 4

The H_0 acidity function in aqueous perchloric acid-sodium perchlorate solutions

$HClO_4$	Added $NaClO_4$	H_0	$HClO_4$	Added $NaClO_4$	H_0
moles per liter	*moles per liter*		*moles per liter*	*moles per liter*	
6	0	−3.05	2	4	−1.84
5	1	−2.77	1	5	−1.46
4	2	−2.47	0.5	5.5	−1.11
3	3	−2.13	0.3	5.7	−0.85

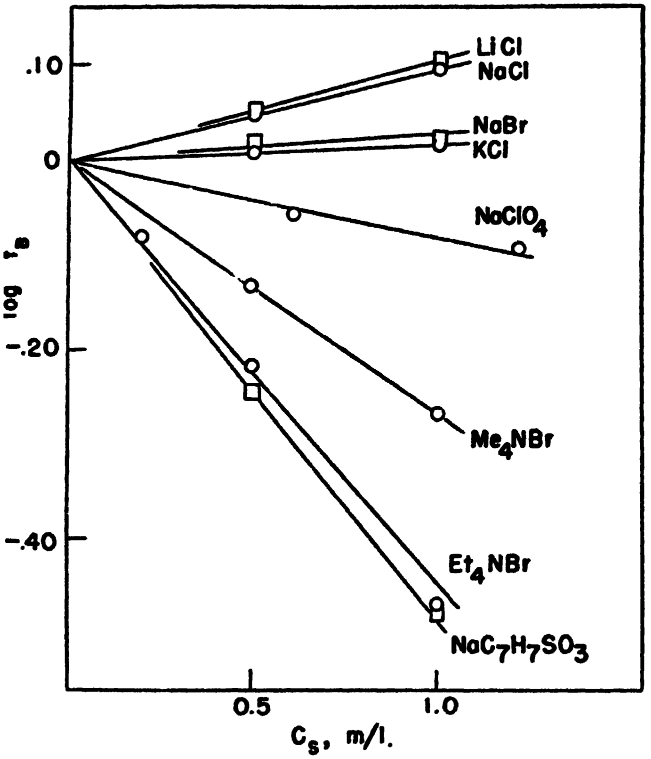

FIG. 7. Salt effects on the activity coefficient of *p*-nitroaniline (59, 65, 77)

values of table 1.[5] The striking point is the very large increase in $-H_0$ caused by the salt. For example, the addition of 5 *M* sodium perchlorate to 1 *M* perchloric acid causes $-H_0$ to increase from 0.22 to 1.46. Qualitatively an increase is to be expected according to equation 8, since the added salt should "salt out" the indicator; i.e., log f_B should increase and, as before, the term log (f_{H^+}/f_{BH^+}) should also increase with added electrolyte.

It is well known that the influence of salts on the activity coefficients of non-

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[5] The agreement between Harbottle's H_0 value of −3.05 for 6 *M* perchloric acid and the "best value" from table 2 of −2.84 is not very satisfactory, considering that the same indicators were used for the two studies.

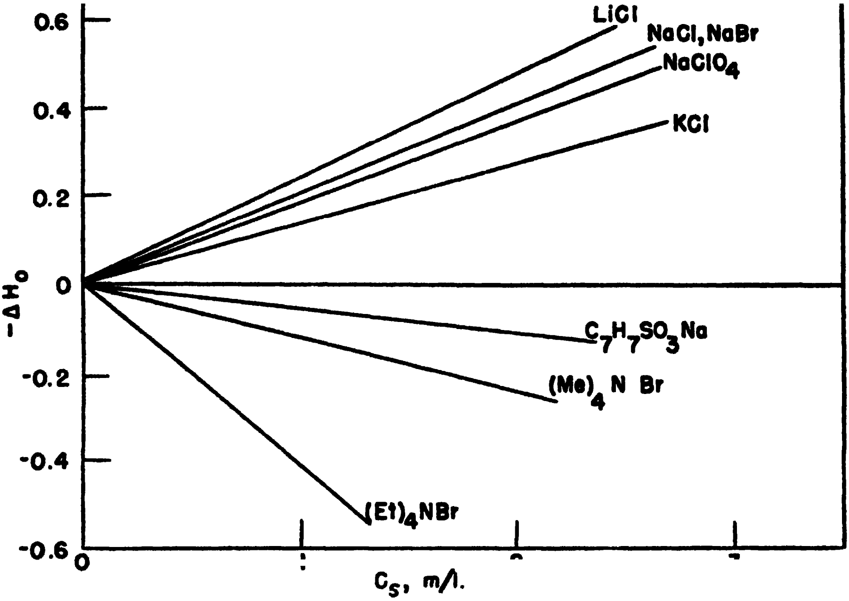

FIG. 8. Salt effects on H_0 of 0.1 M hydrochloric acid (65, 77). The indicator is *p*-nitroaniline.

electrolytes depends markedly on the salt (64, 71). Figure 7 shows, for example, how salts affect the activity coefficient of the indicator base *p*-nitroaniline, as determined from solubility measurements (59, 65). One obtains typically a linear relationship between log f_B and the salt concentration, C_s, and while the particular order observed in figure 7 is more characteristic of nitro compounds than of nonelectrolytes in general (64), the tendency is for the larger ions to salt in (more negative effect on log f_B) as compared with the smaller ions. One would therefore certainly predict that salts would have specific effects on H_0 through the log f_B term in equation 8 and perhaps through the term log (f_{H^+}/f_{BH^+}) as well.

Paul (77) has reported studies of salt effects on H_0 with several indicators in 0.01, 0.1, and 1 M aqueous hydrochloric acid solutions. The results for *p*-nitroaniline in 0.1 M hydrochloric acid are summarized in figure 8. One sees that the effects of the various salts are indeed specific and follow much the same order as their effects on log f_B; the conspicuous differences between the salt orders occur in the cases of sodium perchlorate and sodium *p*-toluenesulfonate, both of which have relatively large anions and both of which show a larger relative tendency to salt in the neutral base than would be suggested by their effects on H_0.

Since both the salt effect on log f_B and the salt effect on H_0 are linear in the salt concentration, C_s, one may profitably compare the slopes of the corresponding $-\Delta H_0$ vs. C_s and log f_B vs. C_s relationships;

$$-\Delta H_0 = \alpha C_s \tag{9}$$

$$\log f_B = k_3 C_s \tag{10}$$

TABLE 5

Comparison of salt effects on $-H_0$ and on log f_B for the indicator p-nitroaniline in 0.1 M hydrochloric acid

Salt	Slope, α, Equation 9[*] (from Figure 8)	Slope, k_B, Equation 10[*] (from Figure 7)	Difference
NaBr	0.205	0.040	0.17
LiCl	0.245	0.082	0.16
NaCl	0.205	0.072	0.13
KCl	0.145	0.030	0.12
$(CH_3)_4NBr$	−0.12	−0.272	0.15
$(C_2H_5)_4NBr$	−0.41	−0.44	0.03
$C_7H_7SO_3Na$	−0.06	−0.51	0.45
$NaClO_4$	0.180	−0.082	0 26

[*] The reference solution for $-\Delta H_0$ is 0.1 *M* hydrochloric acid; the reference for Δ log f_B is the saturated solution of the indicator in pure water. The difference is not significant for the present purpose.

where in this case

$$\Delta H_0 = (H_0)_{0.1\ M\ \mathrm{HCl} + \mathrm{salt}} - (H_0)_{0.1\ M\ \mathrm{HCl}}$$

and where k_B is the conventional salting-out parameter (64). The comparison is shown in table 5. The last column gives the difference between α and k_B, which according to equation 8 must represent the slope of the hypothetical log (f_{H^+}/f_{BH^+}) vs. C_s relationship at the given acid concentration. One sees that this latter quantity is positive in magnitude for the given indicator and is considerably less dependent on the particular electrolyte than is the effect on H_0 itself. We may reasonably conclude that increasing the acid concentration itself in the absence of added salt will have a similar effect on this term, thus accounting in part at least for the difference between $-H_0$ and log C_{H^+} at high acid concentrations, as noted in Section III,A.

Paul (77) has also reported that the salt effects on H_0 are dependent on the indicator. Thus the slope, α, of the $-\Delta H_0$ vs. C_s relationship is about 20 per cent greater for diphenylamine than for *p*-nitroaniline. The difference consists almost entirely of an observed difference in the term log f_B. Such specific effects on the different indicators are not observed with the strong acids (sulfuric, perchloric, hydrochloric, nitric). It is likely that their "salt" effects on log f_B are small in magnitude (64, 65) and therefore show little relative variation from one indicator to another.

Another study of the influence of salts on the acidity function has been reported by Moiseev and Flid (29, 73). They have used the single indicator *p*-nitroaniline and discuss their results in terms of the measured variation in the indicator ratio, C_{BH^+}/C_B. They utilize the equation

$$y = \mathrm{p}K_{BH^+} + \log C_{H^+} + L\mu \tag{11}$$

where y is defined as log (C_{BH^+}/C_B), μ is the ionic strength due to the added salt (in moles per liter units), and L is the slope of y vs. μ.[6] From the definition of

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[6] An abstract (Chemical Abstracts **49**, 7327 (1955)) erroneously states that in the paper by Moiseev and Flid (73) "an acidity function y is defined as $y = \log C_{H^+} + \mathrm{p}K_a + L\mu$." Actually, y is defined as log $(C_{BH}{}^+/C_B)$ and is determined from experiment. The unknown defined by this equation is the parameter L for the salt effects.

H_0 it follows that for 1:1 electrolytes at a constant value of C_{H^+}, the slope L and the slope α of equation 9 should be identical. In one set of experiments Moiseev and Flid utilize a constant acid concentration of 1.075 *M* hydrochloric acid and determine the effect on y of adding potassium chloride (1.57–2.65 *M*), calcium chloride (0.517–1.02 *M*), and magnesium chloride (0.35–1.6 *M*). These three salts all give a linear plot of y vs. $\Delta\mu$ and lead to the same L value of 0.10. The values of y for solutions of hydrochloric acid itself, with concentrations of from 0.86 to 3.2 *M*, are also fairly well in agreement with equation 11, using this same value of $L = 0.10$. Put another way, one can approximately treat the departure of $-H_0$ from log C_{H^+} for hydrochloric acid as a salt effect of similar magnitude to that caused by potassium chloride.

These studies with hydrochloric acid are at least roughly in agreement with those of Paul (77). For example, using *p*-nitroaniline as the indicator, Paul reports for the addition of potassium chloride to solutions of 0.1 *M* hydrochloric acid a slope of $-\Delta H_0$ vs. C_s of 0.14; with the indicator *o*-nitroaniline and solutions of 1 *M* hydrochloric acid containing added potassium chloride the slope is again 0.14. This value is to be compared with Moiseev and Flid's value of $L = 0.10$. Paul also reports (77, Fig. 3) that the "salt effect" of hydrochloric acid itself on values of H_0 (using *o*-nitroaniline as indicator) is very similar to the salt effects of potassium and sodium chlorides. However, Paul does emphasize the specificity of salt effects, whereas Moiseev and Flid at least implicitly assume an L value which is independent of choice of salt. Presumably this difference of viewpoint results from the fact that Paul deliberately studied salts with widely differing anions and cations and hence found widely different salt effects.

Moiseev and Flid have made similar studies with sulfuric acid, alone and with added salts (both sulfates and nonsulfates). Most sulfates cause a decrease in the observed values of y, obviously because of a lowered acidity due to the reaction $H^+ + SO_4^= = HSO_4^-$. One exception is mercuric sulfate, whose addition causes a marked increase in y. This is interpreted in terms of formation of the complex anion, $Hg(SO_4)_2^=$.

D. "Weak" acids

The acids considered in this section are in fact somewhat stronger than phosphoric and hydrofluoric acids, which were discussed earlier. This is evident from table 6, which compares pK values for all of these acids. The characteristic of the present group, then, is not their weakness as such but the observed lack of dependence of H_0 on concentration which they all exhibit at intermediate concentration ranges. Figure 9 is a plot of the H_0 data and includes the curve for perchloric acid from figure 4 for comparison.

The data for dichloroacetic acid and potassium hydrogen sulfate are those of Bell and Brown (8). The only correction has been to subtract 0.12 from their recorded H_0 values to make them consistent with the pK_{BH^+} values in table 1. The data for trichloro- and trifluoroacetic acids (83) have been recalculated to molar concentrations from the original mole-fraction basis[7] and have been

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[7] Densities for aqueous trichloroacetic acid solutions at 25°C. are given in the *International Critical Tables*, Vol. III, p. 111. Densities for solutions of trifluoroacetic acid

TABLE 6

Ionization constants of weak electrolytes

Acid	pK_a	T	Reference	Acid	pK_a	T	Reference
		°C.				°C.	
CF_3COOH	Strong	25	(56)	$CHCl_2COOH$	0.85	0	(84)
					(1.06)*	25	
CCl_3COOH	0.64	25	(84)	H_3PO_4	2.12	25	(80)
$KHSO_4$	2.00	25	(84)	HF†	3.17	25	(17, 79)

* Estimated.

† Broene and DeVries (17) give $K = 4.0$ for the reaction

$$F^- + HF = HF_2^-$$

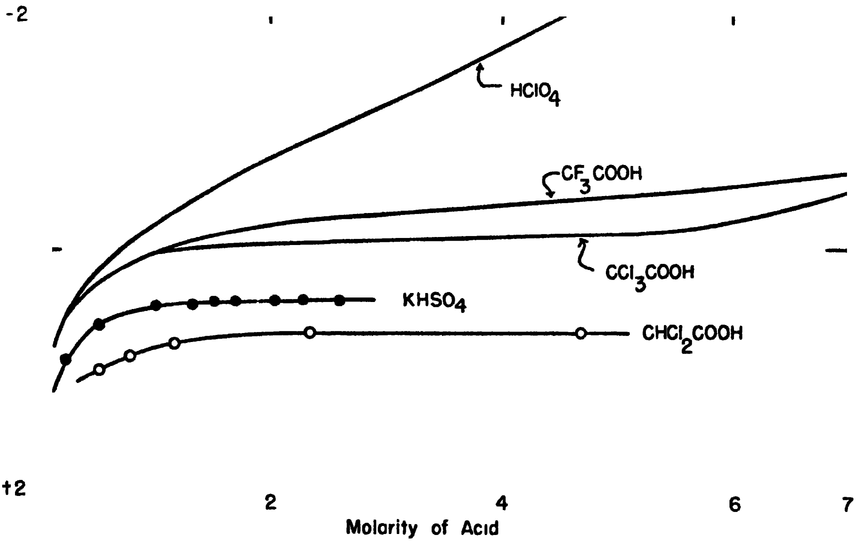

FIG. 9. H_0 for aqueous solutions of weak acids (8, 83)

corrected to be in accord with the pK values of table 1. Besides these weak acids, measurements of H_0 have been obtained for a wide range of aqueous solutions of formic, acetic, chloroacetic, methanesulfonic, and orthophosphorous acids (6).

Hammett and Paul (51) give three H_0 determinations for solutions of trichloroacetic acid. These show a similar lack of dependence of H_0 on concentration but fall about 0.5 unit below the curve of figure 9. This disagreement stands unexplained.

At concentrations of around 0.2 M, the relative acid strengths as judged from figures 4 and 9 for the weak acids are in reasonable accord with the pK values of table 6. The largest H_0 values (lowest acidities) are for the weakest acids, phosphoric and hydrofluoric. The strongest acids, trifluoroacetic acid and trichloroacetic acid, give more acid solutions. Only potassium acid sulfate falls somewhat out of line.

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were estimated by the authors from those of trichloroacetic acid by taking into account the relative densities of the two acids in the liquid state.

The situation at higher concentrations (2 to 6 M) is quite different. The $-H_0$ values for phosphoric and hydrofluoric acids increase steadily with concentration (figure 4). In contrast, the acids of figure 9 exhibit broad concentration ranges where the acidity function changes almost not at all. As a result the relative acidities for, say, 6 M solutions are no longer even approximately in line with the pK values of table 6. A qualitative (and tentative) explanation for these results can be given in terms of the definition of H_0 as written in equation 8. Because of their small size and compact structure it is reasonable that phosphoric and hydrofluoric acids, whether ionized or nonionized, will have little effect on f_B, the activity coefficient of the uncharged indicator base, B. Hence the last term on the righthand side of equation 8 will not change much with concentration, and $-H_0$ will increase with acid concentration owing to an increase in the log C_{H^+} term and probably also to an increase in log (f_{H^+}/f_{BH^+}). The situation for the large acid molecules—dichloroacetic, trichloroacetic, and trifluoroacetic acids—should be quite different. One can expect "salting in" of the base, B, by both the ionized and the nonionized forms of the acid (64, 65, 71).[8] The result will be a decrease in the value of the term log f_B with increasing concentration of acid. The data of figure 9 suggest that this decrease roughly equals the increase in $-H_0$ from the terms log C_{H^+} and log (f_{H^+}/f_{BH^+}), leading to the approximate lack of dependence of H_0 on the concentration. Indirect support for the suggestion that the organic acids themselves will "salt in" the indicator (decrease f_B) and hence lower the indicator acidity is available from the work of Bartlett and McCollum (2), who find that the addition of small amounts of isopropyl alcohol to sulfuric acid–water mixtures causes a marked decrease in $-H_0$, as measured with the indicator 2,4-dinitroaniline.

The implication of this explanation is that for aqueous solutions of weak acids the experimental values of the acidity function may vary considerably for different indicators. This is so because the salting-in contribution, i.e., changes in log f_B, will vary with the nature of B and it is unlikely that changes in log (f_{H^+}/f_{BH^+}) will entirely compensate. In fact, the agreement between results for different indicators is not very good for either trifluoroacetic acid or trichloroacetic acid (83). With the former the data from *o*-nitroaniline are about 0.15 unit above those from *p*-nitroaniline and 4-chloro-2-nitroaniline. With trichloroacetic acid the data for *o*-nitroaniline lie about 0.1 unit below those for *p*-nitroaniline. Similar discrepancies are shown in table 1 for solutions of phosphoric acid. These facts cast doubt on the generality and utility of the H_0 function for such systems and further study is highly desirable.

IV. SOLUTIONS IN NONAQUEOUS AND MIXED SOLVENTS

One of the more important properties of the acidity function is that it can be utilized in nonaqueous solutions and the resulting acidities are automatically referred to the dilute aqueous reference state. However, it is also true that there are added problems for either nonaqueous or mixed solvents, particularly for solvents with low dielectric constants, and for these cases it is generally necessary to reëxamine the validity of the acidity function concept. This point of view has been emphasized by Grunwald and coworkers (35, 37, 38) and by Bates and Schwarzenbach (5), particularly as a result of studies with ethanol–water mixtures. It will be considered in detail in Section IV,D.

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[8] For brevity (and for want of a better term) the phrase "salting in" will be used to denote a decrease in the activity coefficient of an uncharged species, whether this decrease is caused by increased concentration of an electrolyte or of another nonelectrolyte molecule.

A. Formic acid

H_0 measurements in anhydrous formic acid were reported by Hammett and Deyrup (47) for solutions of benzenesulfonic acid between 0.005 and 0.15 *M*, for sulfuric acid within the same concentration range, for sodium formate between 0.006 and 0.1 *M*, and for aniline within the same range. This solvent has a high dielectric constant, 58.5 at 16°C. (70). Sodium formate and aniline behave toward the indicators as completely ionized strong bases; sulfuric acid behaves as a completely ionized monobasic acid, while benzenesulfonic acid at 0.1 *M* concentration is only slightly weaker. These findings are consistent with potentiometric titration data in formic acid observed by Hammett and Dietz (49). The H_0 values range from -0.22 (corrected to the present $\mathrm{p}K_{\mathrm{BH^+}}$ scale) in 0.10 *M* sodium formate to -4.04 in 0.15 *M* benzenesulfonic acid. Self-ionization of the solvent is sufficiently extensive so that its own H_0 could be determined directly by indicator measurements; it has the value $H_0 = -2.21$ (47).

Aside from the generally high level of acidity, the most significant aspect of the results is the agreement of the $\mathrm{p}K_{\mathrm{BH^+}}$ values observed for the various indicators in formic acid with the values observed in aqueous solutions of strong acids (see table 1). This lends conviction to the idea that the different indicators are in fact measuring the same property of the solutions and that H_0 values in this medium are directly referable to values obtained in aqueous solutions.

In dilute solutions of a sufficiently strong acid, A, in a relatively basic solvent, S, one can define $\mathrm{p}K^{\mathrm{S}}_{\mathrm{BH^+}}$ values for the indicators as follows:

$$\mathrm{p}K^{\mathrm{S}}_{\mathrm{BH^+}} = \lim_{C_{\mathrm{A}}\to 0}\left[\log\frac{C_{\mathrm{BH^+}}}{C_{\mathrm{B}}} - \log C_{\mathrm{H^+}}\right]_{\text{in S}} \tag{12}$$

where $C_{\mathrm{H^+}} = C_{\mathrm{A}} - C_{\mathrm{BH^+}}$ and C_{A} represents the stoichiometric concentration of A in S. For a given indicator the connection between $\mathrm{p}K^{\mathrm{S}}_{\mathrm{BH^+}}$ and $\mathrm{p}K_{\mathrm{BH^+}}$ (defined as previously for the aqueous reference state) is then as follows:

$$\mathrm{p}K^{\mathrm{S}}_{\mathrm{BH^+}} - \mathrm{p}K_{\mathrm{BH^+}} = \log\frac{f^0_{\mathrm{B}}f^0_{\mathrm{H^+}}}{f^0_{\mathrm{BH^+}}} \tag{13}$$

where the activity coefficients represent the limiting values at infinite dilution in S relative to their values at infinite dilution in water. Application of equation 12 to the data of Hammett and Deyrup for solutions of the strong acids benzenesulfonic and sulfuric in formic acid leads, after allowance for the self-ionization of the solvent, to the empirical conclusion:

$$\mathrm{p}K^{\mathrm{HCOOH}}_{\mathrm{BH^+}} - \mathrm{p}K_{\mathrm{BH^+}} = 5.10$$

That is, $pK^S_{BH^+}$ for the conjugate acid of an uncharged base, B, in formic acid solutions may be calculated from the corresponding value of pK_{BH^+} in water simply by adding 5.10. The large magnitude of this number reflects the highly acid character of anhydrous formic acid as a solvent.

Values of H_0 for ether–formic acid mixtures of from zero to 65 per cent ether are reported by Plattner, Heilbronner, and Weber (82). As would be expected, the acidity drops sharply when ether is added to formic acid.

B. Acetic acid

Acetic acid has a much lower dielectric constant than formic acid (6.2 at 25°C. (94) as compared with 58.5). It is not surprising therefore to find that "strong" acids dissolved in this medium do not behave simply as completely ionized solutes; ion-pair association is probably widespread and the concept of hydrogen-ion concentration loses much of its significance. The various acids, in other words, show a much higher degree of specificity than is shown in media of higher dielectric constant or higher basicity. The problem of ion pairs in acetic acid has recently been discussed in some detail by Kolthoff and Bruckenstein (58). These authors have made studies with such indicators as *p*-naphtholbenzein and dimethylaminoazobenzene in anhydrous acetic acid and also in acetic acid containing small amounts of water; they conclude that not only ion pairs but also ion triplets and ion quadruplets must be present. Nevertheless indicator studies may be readily carried out and are capable of yielding useful information.

The most extensive set of H_0 measurements is by Hall and Spengeman (41), who investigated solutions of sulfuric acid in anhydrous acetic acid up to 8 *M* concentration by optical colorimetry. Their results (selected values) are shown in figure 10; results in substantial agreement for sulfuric acid concentrations between 0.002 and 1.6 *M* have been reported by Paul and Hammett (78). Gold and Hawes (32) have also obtained very similar results with the one indicator, 4-chloro-2-nitroaniline, at sulfuric acid concentrations between 0.18 and 0.95 *M*, using a spectrophotometer. In figure 10 "best" values of pK_{BH^+} from table 1 have been used for the indicators. One sees that a reasonably uniform H_0 scale is obtained for the various indicators with the exception of 2,4-dichloro-6-nitroaniline and *N*,*N*-dimethyl-2,4,6-trinitroaniline. The lack of parallelism of the results for the latter with the results for the other indicators is also shown in aqueous sulfuric acid solutions (see figure 1) and presumably reflects a fundamental unsuitability of this indicator. The H_0 values for 2,4-dichloro-6-nitroaniline run parallel with those obtained for the other indicators, but they are displaced by about 0.4 unit in the direction of lower apparent acidity.

One of the noteworthy aspects of the results with acetic acid is the relatively high acidity at given sulfuric acid concentrations as compared with aqueous solutions; a 1 *M* sulfuric acid solution in anhydrous acetic acid, for example, has $H_0 = -3.01$ as compared with $H_0 = -0.26$ in 1 *M* aqueous solution. This high acidity is in qualitative agreement with electrometric "pH" measurements obtained originally by Hall and Conant (39) using the chloranil electrode, although the indicators actually measure a rather different property of the solutions.

If one plots $-H_0$ against log C_A for solutions of sulfuric acid in acetic acid at concentrations below 0.1 *M*, a straight line with unit slope is obtained, corresponding to a limiting value of $H_0 + \log C_A = -2.69$ in infinitely dilute solution. This is the sort of behavior one would expect in ideal dilute solution if sulfuric acid were a strong 1:1 electrolyte. However, if one uses similar data for solutions of perchloric acid in anhydrous acetic acid (61) the limiting value of $H_0 + \log C_A$ is quite different, -4.00. Further studies (93) with a variety of "strong" acids in acetic acid containing a small concentration of dissolved water (0.12 per cent by weight) have shown that, for each, $-H_0$ is linear in log C_A with slopes that are close to unity (see figure 11). The lines, however, are markedly displaced from each other. For example, at $C_A = 10^{-3}$ *M*, the value of $-H_0$ for perchloric acid is 1.6 units greater than that for hydrochloric acid. This behavior suggests that one may be dealing with indicator equilibria involving ion pairs rather than simple solvated H^+ ion. Equation 12 appears therefore to be meaningless when applied to acetic acid. It will be of considerable interest to see if the variations in acidity shown in figure 11 lead to comparable variations in rates of acid-catalyzed reactions for these media.

Measurements of H_0 have also been reported for solutions in anhydrous acetic acid of the basic solutes urea and antipyrine and their buffer mixtures with sulfuric acid (40).

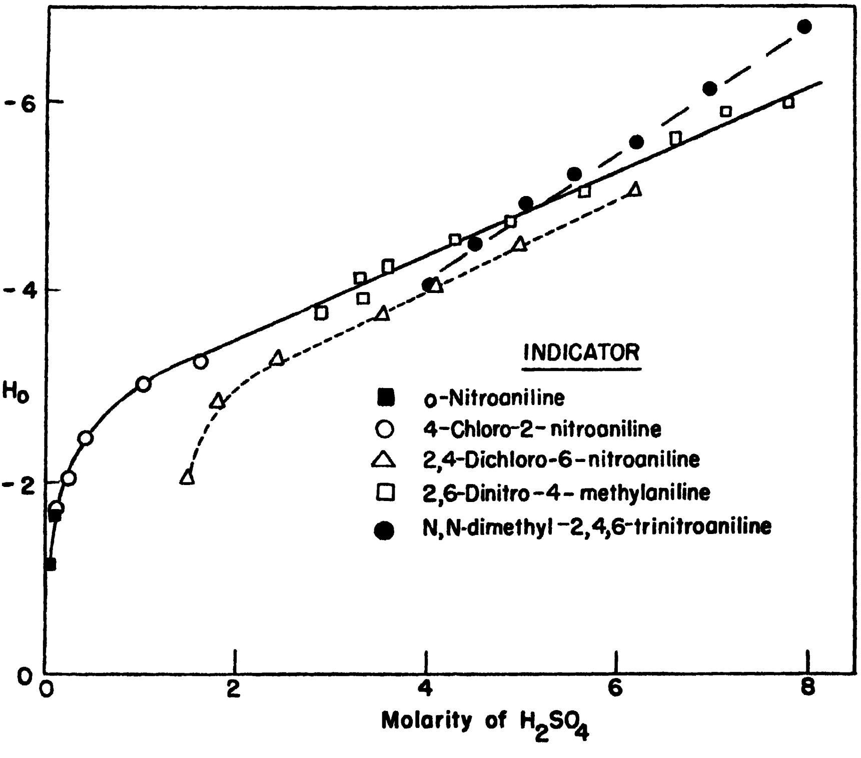

FIG. 10. H_0 for solutions of sulfuric acid in acetic acid (41)

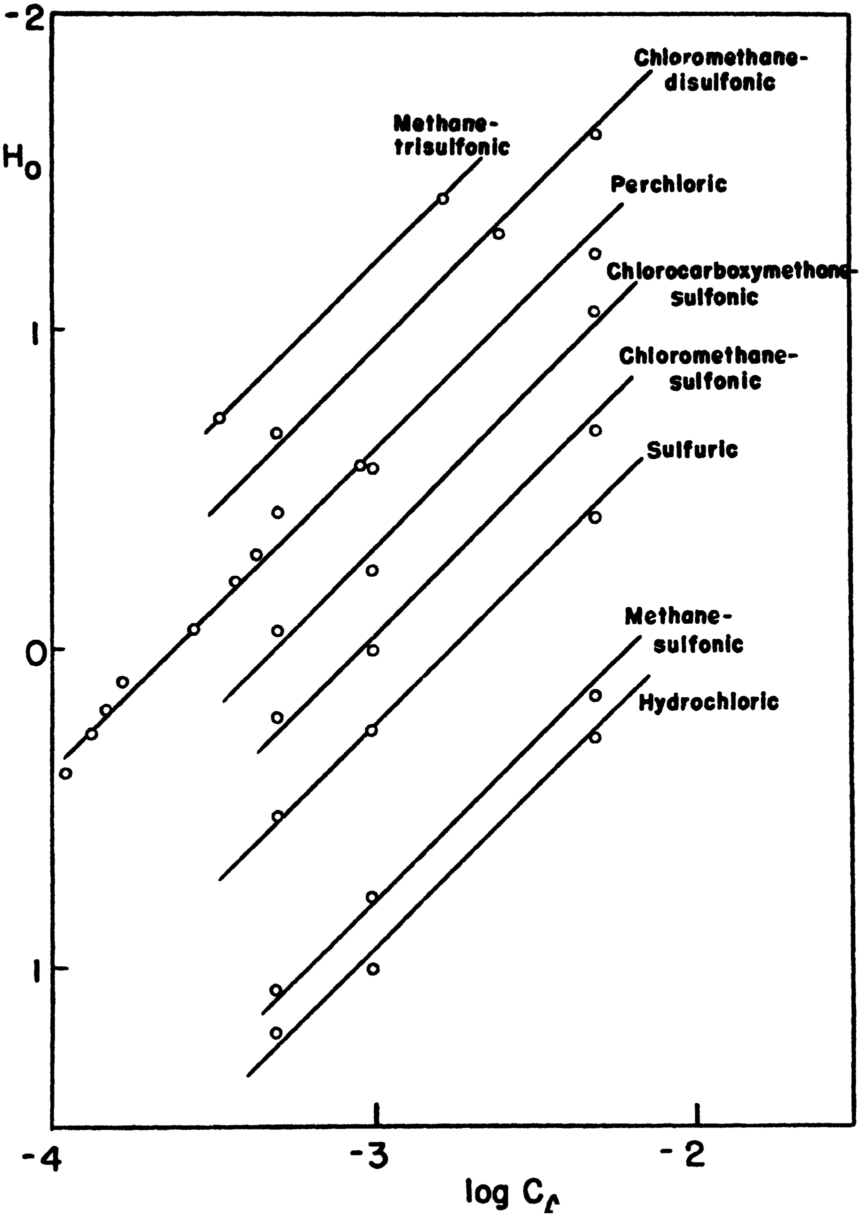

FIG. 11. H_0 for solutions of several acids in acetic acid containing 0.12 per cent water. Straight lines of unit slope have been drawn through the experimental points of Smith and Elliott (93).

The influence of water on H_0 in acetic acid solutions has been investigated for several situations. For solutions which contain a constant concentration of 0.001 *M* perchloric acid, addition of water causes a large decrease in acidity, since H_0 goes from -1.00 to $+1.93$ as the water content increases from 0 to 5

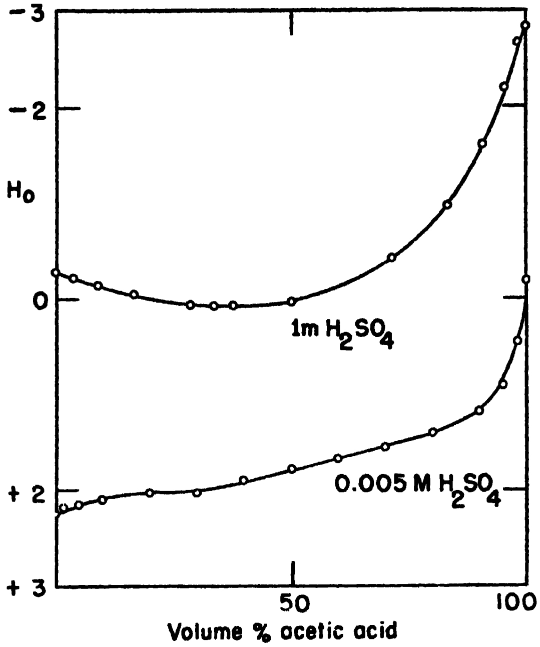

FIG. 12. H_0 for acetic acid-water mixtures containing sulfuric acid (76)

per cent (67). Somewhat similar results are shown for studies of phosphoric acid (concentrations ranging up to 15 per cent) in acetic acid solutions containing up to 6 per cent water (57).[9] Finally, a study is available of both 1 molal and 0.01 normal sulfuric acid in solutions ranging from pure water to pure acetic acid (76). In 0.01 normal sulfuric acid the value of $-H_0$ increases continually from -2.24 to $+0.18$ with increasing acetic acid concentration but in 1 molal sulfuric acid $-H_0$ passes through a shallow minimum at about 38 volume per cent acetic acid (figure 12). This may well be the result of a "salting-in" effect of acetic acid on the neutral indicator molecule, B (as in the case of the substituted acetic acids shown in figure 9). The acidity increases with still higher concentrations of acetic acid because the weaker acid, H_3O^+, is ultimately replaced by the stronger acid, $CH_3COOH_2^+$, while at the same time the decreasing dielectric constant of the medium takes effect (42).

C. Acetic acid–acetic anhydride

Mackenzie and Winter (68) report what they call "apparent H_0 values" for 0.078 *M* perchloric acid in acetic acid–acetic anhydride mixtures of from 20 to 90 volume per cent anhydride. Their conclusion, that the acidity increases with increasing amounts of the anhydride, seems quite reasonable. However, the listed H_0 values are questionable, since the indicator used, 2,6-dimethoxyquinone, apparently reacts with acids in a quite complicated manner to give eventually a doubly charged acidic form. The acetic acid–acetic anhydride system is an important one, and it will be of interest to repeat this work with a more conventional indicator.

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[9] *Note added in proof:* Additional data have been reported for perchloric and sulfuric acids at varying concentrations in acetic acid containing up to 15 per cent by weight of water (85b) and for hydrochloric and sulfuric acids in acetic acid containing 10 per cent by volume of water (76a); the indicators used in these various studies were *p*-nitroaniline, *o*-nitroaniline, and 4-chloro-2-nitroaniline.

D. Ethanol, acetone, dioxane, and their mixtures with water

These three organic solvents are extensively used both in the pure form and when mixed with water and perhaps as a result have been the subject of several studies on the acidity function. They are all characterized by relatively low dielectric constants: 2.2 for dioxane at 25°C. (63); 24.2 for ethanol at 25°C. (70); 19.1 for acetone at 25°C. (1) (for their mixtures with water see reference 1). As a result, a point of major importance is whether the concept of the acidity function can usefully be applied to these systems.

Solutions of hydrochloric acid in ethanol, acetone, and dioxane have been investigated up to 1 *M* acid concentration by Braude (14), using the single indicator *p*-nitroaniline. Similar though less extensive studies with the same indicator have been reported by Eaborn (26) for hydrochloric acid in dioxane–water mixtures and for hydrochloric and perchloric acids in methanol–water solutions. Mixtures containing varying proportions of water with the three solvents ethanol, acetone, and dioxane have been investigated at 0.1 *M* and 1 *M* concentrations of hydrochloric acid by Braude and Stern (16), using the indicators *p*-nitroaniline and *m*-nitroaniline. All measurements were with a spectrophotometer. Judging by the constancy of $H_0 + \log C_{H^+}$ in dilute solutions, hydrochloric acid behaves as a strong acid in ethanol and acetone. The calculated $pK^S_{BH^+}$ values for *p*-nitroaniline are 1.3 and 1.6 for ethanol and acetone, respectively, compared to 0.99 in water. In dioxane, hydrochloric acid apparently behaves as a weak acid, a result consistent with the much lower dielectric constant. Actually, in view of the marked specificities discussed earlier for solutions of strong acids in acetic acid, it is probably unsafe to conclude that solutions in ethanol and acetone are free from similar specific effects.

According to Braude and Stern (15, 16) the effect of water is similar for all three solvents in that $-H_0$ goes through a minimum with changing water concentration at fixed concentration of the acid (0.1 *M* and 1 *M*). Figure 13 shows the results for 0.1 *M* hydrochloric acid (corrected to a pK_{BH^+} value of 0.99 for *p*-nitroaniline). The depth of the minimum is greater in each case than for comparable data in the case of acetic acid (figure 12), but its occurrence probably stems from a similar source. Addition of ethanol, acetone, or dioxane to a water solution of the acid surely tends to decrease the term $\log f_B$ in equation 8, i.e., to "salt in" the neutral base B. Further addition must ultimately increase $\log f_{H^+}$ as the acid ion, H_3O^+, gives way to the stronger acid, SH^+, conjugate with the organic solvent base, S.[10] An alternate view, presented by Braude and

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[10] In a personal communication Professor Braude states that the H_0 value of about 1.4 shown in figure 13 for pure dioxane is actually for dioxane which contains from 0.2 to 0.3

TABLE 7

$pK^{S}_{BH^+}$ *values at 25°C. for ethanol–water solutions* (37)

Acid Cation	Weight Per Cent Ethanol			
	0.0	35	65	100
Anilinium	4.636	4.161	3.799	5.70
p-Toluidinium	5.098	4.642	4.312	6.24
m-Toluidinium	4.77	4.28	3.87	5.78
o-Toluidinium	4.46	3.96	3.56	5.55
N-Methylanilinium	4.839	4.276	3.636	4.86
N,*N*-Dimethylanilinium	5.01	4.30	3.50	4.37
Ammonium	9.26	8.78	8.45	
Monomethylammonium	10.70	10.11	9.58	
Dimethylammonium	10.58	9.95	9.36	
Trimethylammonium	9.79	9.13	8.36	

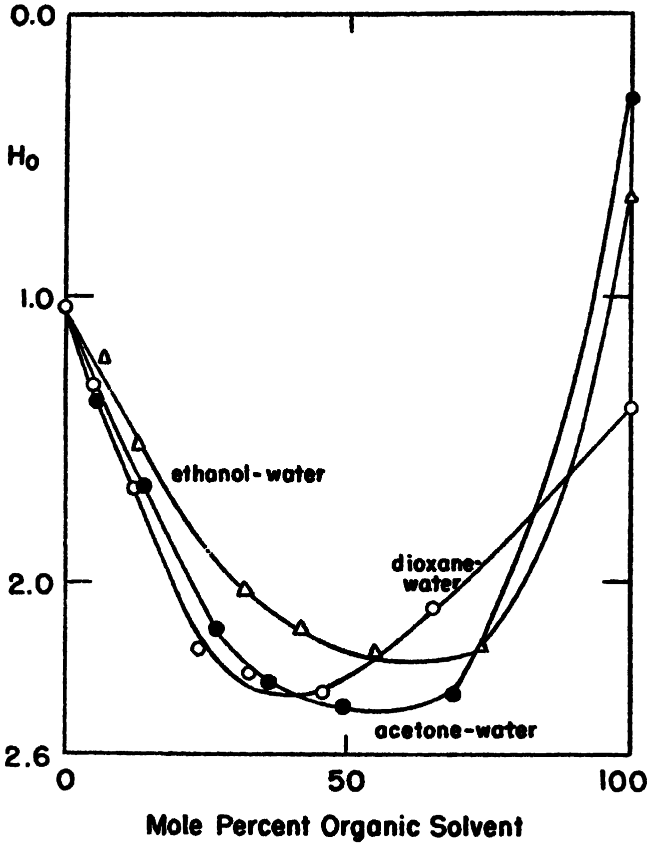


FIG. 13. H_0 in mixed solvents containing 0.1 *M* hydrochloric acid (16)

per cent water. As these last traces of water are removed the indicator acidity drops sharply to values about like those at the minimum of figure 13. Professor Braude concludes that hydrochloric acid in strictly anhydrous dioxane is probably "not only very incompletely dissociated but also incompletely ionized."

Stern, is that the minima stem from disturbance of the hydrogen-bonded structure of water.

Grunwald, Berkowitz, and Gutbezahl (35, 37, 38) have investigated the ionization of various uncharged acids and bases in ethanol–water mixtures by a differential potentiometric method; a similar study has been made in dioxane–water mixtures by Marshall and Grunwald (69). These investigators find that the acid ionization constants, $\mathrm{p}K^{\mathrm{S}}_{\mathrm{BH}}$ or $\mathrm{p}K^{\mathrm{S}}_{\mathrm{BH^+}}$, respectively, at infinite dilution in the solvent S (including the mixed as well as the pure nonaqueous solvents), are displaced from their values in pure water by varying amounts, as shown in table 7. Thus $\mathrm{p}K_{\mathrm{BH^+}}$ for anilinium ion goes from 4.64 in water at 25°C. to 5.70 in pure ethanol, passing through a minimum of about 3.75 at 80 weight per cent ethanol, while the value for *N*-methylanilinium ion goes from 4.84 to 4.86, with a minimum of 3.42 also at about 80 per cent ethanol. From the differences in behavior exemplified by these two they conclude that the H_0 function does not exist in pure ethanol or in the more concentrated ethanol–water mixtures.

This existence test is actually quite drastic, more so than has been considered necessary for the establishment of the H_0 scale in aqueous solutions of strong acids. As one examines the data of Grunwald and coworkers in detail, one notes for example that the simple aromatic amines aniline and the three toluidines are in fact in quite good agreement with changing medium, while divergence from them is most conspicuous on the part of the aliphatic amines and *N*-substituted aromatic amines. The *N*,*N*-substituted amine (i) in figure 1, however, has been found to diverge from the other indicators even in sulfuric acid–water solutions without destroying the validity and usefulness of the H_0 acidity scale in this medium. It is quite possible that a useful H_0 scale can still be constructed even for pure ethanol by the selection of a suitable set of indicators.

Grunwald and coworkers emphasize the importance of testing for the consistency of indicator acidity measurements by the use of several different indicators with overlapping ranges. Outside the dilute aqueous range, indicator studies based on but a single indicator may well involve an unknown contribution on the part of the particular indicator, even when it is of a specified charge type. One therefore has no right to assume that an uncharged base necessarily gives universal H_0 values in mixed and nonaqueous solvents. On the other hand, one may well be able to show on empirical grounds that over a significantly wide range of structural variations in the indicators, an H_0 scale may be established

TABLE 8

H_0 values for water–dioxane mixtures

$c_{\mathrm{HClO_4}}$	H_0 60% Dioxane	H_0 40% Dioxane	H_0 Water	$c_{\mathrm{HClO_4}}$	H_0 60% Dioxane	H_0 40% Dioxane	H_0 Water
moles per liter				*moles per liter*			
0.25	+1.90	+1.43	+0.52	2.5	−0.70	−0.66	−1.01
0.5	+1.40	+1.00	+0.18	3.0	−1.10	−0.99	−1.23
1.0	+0.75	+0.42	−0.22	3.5	−1.48	−1.33	−1.47
1.5	+0.22	+0.03	−0.53	4.0	−1.84	−1.67	−1.72
2.0	−0.26	−0.33	−0.78				

for a given medium within a reasonable degree of consistency, even though individual bases may be found that do not conform exactly with this scale.

Indicator measurements have recently been obtained by Bunton, Vernon, and coworkers (17a) for solutions of perchloric acid in dioxane–water mixtures containing respectively 60 per cent and 40 per cent dioxane by volume. The indicators were *p*-nitroaniline, *o*-nitroaniline, and 4-chloro-2-nitroaniline; the acid concentrations were between 0.2 and 4.5 *M*. Table 8 lists H_0 values calculated by using indicator pK_{BH^+} values from table 1, together with comparison values for aqueous solutions. For both mixed solvents the H_0 values fall nicely on continuous curves. On this basis it appears that a useful H_0 function exists for these solutions. It is of interest to note that at low concentrations of perchloric acid the aqueous solutions show a considerably higher indicator acidity but that for the 4 *M* solutions this difference has essentially disappeared. For both mixed solvents $-H_0$ increases considerably faster than $\log C_{H^+}$ even at 0.5 *M* acid concentration, i.e., at a concentration where the value of $-H_0$ is only about -1.0. This separation of the two acidity measures at such low acidities may be of considerable advantage for applications to reaction kinetics.

A comparison of these data with those of Braude (14) for solutions of hydrochloric acid in the same solvents suggests that for 0.1 *M* solutions the indicator acidities for perchloric and hydrochloric acids are closely similar. For 1 *M* solutions, however, hydrochloric acid shows a considerably lower indicator acidity; the H_0 values for 1 *M* hydrochloric acid in 60 per cent and 40 per cent dioxane are, respectively, 1.28 and 0.93.

Indicator acidities have also been reported by Kreevoy (58a) for solutions of perchloric acid in "50 per cent by volume" dioxane–water with 4-chloro-2-nitroaniline as the indicator. The data are in general agreement with those of table 8, but a precise comparison cannot be made since the procedures for preparing the solutions are different. Bunton and his associates maintained the stated volume proportion of dioxane and water for all solutions; Kreevoy mixed equal volumes of dioxane and of an aqueous perchloric acid solution.

The same three indicators have been applied to solutions of methanesulfonic acid in anhydrous methanol (17a). For this system the apparent H_0 value depends markedly on choice of indicator and as a consequence a useful acidity function scale is not available. In view of the discussion in Section III,D, it is quite likely that this failure is a result of the choice of acid solute rather than of the solvent. The large anion of methanesulfonic acid will probably lead to extensive salting in of the indicators, and the extent of this will be expected to vary with the indicator. In spite of this difficulty, H_0 values from the three indicators for dilute solutions of the acid are in rough agreement and lead to an approximate value of $H_0 = 0.1$ for 0.25 *M* methanesulfonic acid in methanol. The implication is that methanol is a decidedly more acid solvent than any of those in table 8.

Bates and Schwarzenbach (5) have reported an interesting comparison of acidity measures for ethanol–water mixtures with particular emphasis on the acidity functions H_0 and H_-. They have employed three different solutions: a mixture of 0.002 *m* hydrochloric acid and 0.008 *m* sodium chloride; an acidic buffer with 0.02 *m* acetic acid, 0.01 *m* sodium acetate, and 0.005 *m* sodium chloride; a basic buffer with 0.002 *m* triethanolamine and 0.004 *m* triethanolamine hydrochloride. They have measured the following acidities: H_0 using aromatic amine indicators; H_- using nitrophenols and also dimedon as indicators; conventional pH using a cell with a liquid junction and calomel reference electrode; the acidity pw⊕, defined as

$$\text{pw}\oplus = \frac{F(E^A - E_0^W)}{2.3RT} + \log C_{Cl^-}$$

where E^A is the potential of the cell

$$\text{Pt, H}_2 \mid \text{test solution} \mid \text{AgCl(s), Ag(s)}$$

and E_0^W is the standard potential for the same cell in water, i.e., for an aqueous hydrochloric acid solution of unit activity. This last acidity is equivalent to $-\log a_{H^+} f_{Cl^-}$. Data for the hydrochloric acid–sodium chloride solutions are given in figure 14. The H_0 values are from measurements with the indicator *m*-nitroaniline (using $pK_{BH^+} = 2.57$); the H_- values are from the use of 4-chloro-2,6-dinitrophenol ($pK_{BH} = 2.97$). The point of major interest is the different behavior of the various functions. The H_0 function shows a minimum in acidity at an intermediate ethanol concentration, very similar to that of figure 13. The functions H_- and pH(conv) both show slight minima. They give similar values of the acidity over most of the range but lead to quite different acidities for pure ethanol. The function pw⊕ shows a steadily increasing acidity.

The different behavior of the various acidity scales is, of course, the expected result, since both the methods of measurement and the quantities involved are

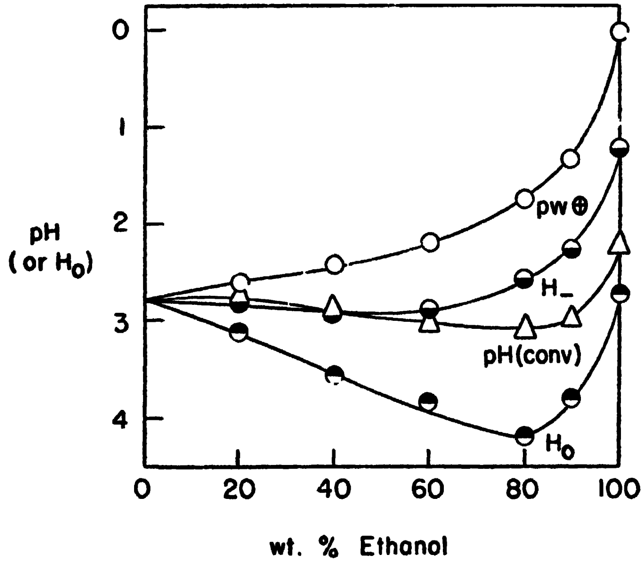


FIG. 14. Various acidity functions in ethanol–water mixtures containing 0.002 *m* hydrochloric acid and 0.008 *m* sodium chloride (5).

quite different. The data very nicely point up the fact that there is no single, uniquely good measure of acidity. There are a variety of them, and any preference depends on such things as ease of measurement and ultimate application. As an example, H_0 is an obvious function to apply to the kinetics of an acid-catalyzed reaction of an uncharged molecule, whereas equally obviously H_- might apply to the kinetics of an acid-catalyzed reaction of a negatively charged ion.

Bates and Schwarzenbach conclude from their studies that the "acidity function" is not useful for solutions of low dielectric constant. This conclusion seems somewhat premature, since for no one of the solutions is H_0 measured with more than one indicator. It is true that the H_0 and H_- acidity functions show different trends with changing ethanol concentration (see figure 14), but there is actually no reason to expect these functions to show similar behavior.

E. Nitromethane

Solutions of sulfuric, hydrochloric, and methanesulfonic acids in nitromethane were investigated by Smith and Hammett (92). They studied also buffer mixtures of sulfuric acid with pyridine. The values of ΔpK for several of the indicators of figure 1 were determined in nitromethane solutions and were found to be in close agreement with the values obtained in aqueous solutions of strong acids.

Between 0.005 and 0.03 M concentration $-H_0$ for the sulfuric acid solutions increases linearly with log C_A but with a slope of 1.76. The $-H_0$ value for a 0.01 M solution of sulfuric acid is about 3.2, indicating much higher acidity than at a similar concentration in water. For hydrochloric acid, $-H_0$ between 0.02 and 0.15 M concentration likewise increases linearly with log C_A, at the same slope of 1.76, but the $-H_0$ values at equal concentrations are displaced about 4.1 units below those for sulfuric acid. The buffer solutions also showed behavior very different from that of aqueous solutions; with a fixed ratio of acid to base, for example, $-H_0$ was found to increase linearly with the logarithm of the total buffer concentration, the slope of the relationship having the same order of magnitude as that found between $-H_0$ and log C_A for the unbuffered acids.

Nitromethane has a rather high dielectric constant, 35 at 25°C. (95), but it apparently has very little capacity for ion solvation; in this latter respect it differs from the oxygen-base solvents such as water, ethanol, acetone, etc. One is therefore dealing with solutions in which ion association is prevalent, not as a consequence of uncommonly strong interionic attraction but rather as a consequence of low solvation energy. There is little experience in terms of which to interpret the behavior of such solutions. The indicators at any rate appear to be measuring a real property of the solutions, and further study of this medium is desirable.

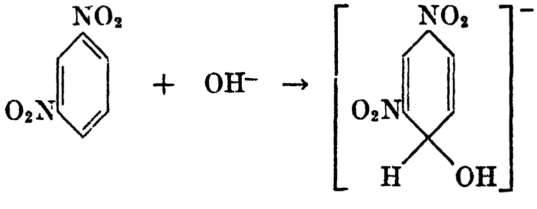
V. RELATED ACIDITY FUNCTIONS

A. H_+ and H_- functions

It was noted in the introduction that other acidity functions closely related to H_0 can be defined according to the charge type of the indicator base. A few studies have been made with H_+ and H_-, but neither has had as extensive development as has H_0. In fact there have not yet been enough studies with varying indicators to be certain that useful H_+ and H_- acidity functions can be developed.

Schwarzenbach and Sulzberger (91) determined H_- acidities at 20°C. for aqueous solutions of sodium and potassium hydroxide ranging from 0.1 *M* to saturated. The indicators were various glutacondialdehyde derivatives, for example, indigo. They were used as solutions in inert media rather than being added directly to the aqueous alkali solutions. A somewhat similar study was made by Deno (21) for aqueous hydrazine solutions ranging from 5 to 60 per cent by weight. The indicators were such compounds as 3,6-dinitrodiphenylamine and 4,4′,4″-trinitrotriphenylmethane. The list includes none of those used by Schwarzenbach and Sulzberger, so that no direct comparison of the two scales can be made. Deno's data cover the range from $H_- = 11.2$ at 5 per cent hydrazine (11.2 is the pH of this solution) to $H_- = 15.9$ at 60 per cent hydrazine. There is no firm evidence that the H_- function for this system is independent of choice of indicator but the system is *a priori* a favorable one, since hydrazine has a notably high dielectric constant of 51.7 at 25°C. (97).

A very similar study has been reported for the system water–ethylenediamine (86). The indicators include such compounds as 3-nitrocarbazole and 2,4-dinitroaniline. The resulting acidity function is stated to cover the range $H_- = 13$ for 15 weight per cent ethylenediamine to $H_- = 18$ for 70 per cent ethylenediamine. However, the H_- values for the high end of the scale are very doubtful, since the data result from the use of *m*-dinitrobenzene as the indicator and it seems quite unlikely that this molecule will lose a proton in 70 per cent aqueous ethylenediamine. A more probable source of a color change for this molecule in basic solution is some such reaction as



Schaal (86) used three of the same indicators that were used by Deno: *p*-nitrobenzyl cyanide, 3,6-dinitrocarbazole, and 3-nitrocarbazole. For the former Schaal reports a pK_{BH} value of 13.45, which is very close to the value of 13.43 reported by Deno and also close to the value of 13.4 obtained from studies in aqueous alkali (96). With 3,6-dinitrocarbazole, which was studied in fairly dilute solutions of ethylenediamine, Schaal reports $pK_{BH} = 13.10$, in good agreement with Deno's value of 13.07. However, with 3-nitrocarbazole Schaal reports $pK_{BH} = 15.10$, whereas Deno gives the value 14.16. This large discrepancy casts considerable doubt on the assumption that these H_- scales are independent of the indicator used and makes it imperative that this be tested by studies with other indicators.

The system water–ethanolamine has also very recently been investigated with some of the same indicators (70a). The value of H_- is reported to increase continuously from 12.05 for 5 per cent ethanolamine to 15.35 for 100 per cent ethanolamine.

Two fairly explicit comparisons have been made of the H_- and H_0 scales. One is included in the study by Bates and Schwarzenbach (5) which was discussed in a previous section (see figure 14). Comparisons were made of H_- and H_0 for three kinds of solutions, hydrochloric acid–sodium chloride, a triethanolamine buffer, and an acetate buffer. Each comparison was for solvent mixtures varying from pure water to pure ethanol. For the first two kinds of solutions the measurements involved only a single amine indicator for H_0 and a single phenol indicator for H_-. In both cases the trends of H_0 and H_- with increasing concentration of alcohol were quite different. For the acetate buffer, H_- as measured with 2,4-dinitrophenol was very similar to H_0 as measured with *p*-chloroaniline. However, a second set of H_- measurements was made with dimedon as the indicator and the results were very different from those for the nitrophenol. In this case at least the H_- function for ethanol–water mixtures is strongly dependent on choice of indicator. It is quite possible that for a solution which contains a weak acid or base the same would be true for H_0.

Another comparison of H_0 and H_- is that of Randles and Tedder (83), who studied aqueous solutions of trifluoroacetic acid and trichloroacetic acid, using as indicators the uncharged bases *o*- and *p*-nitroaniline and the negatively charged picrate ion. The pK_{BH} for the latter of -0.08 (on a scale where pK_{BH^+} for *p*-nitroaniline is 0.99) was chosen so that the H_0 and H_- scales coincided in the dilute region. Above a concentration of about 1.5 *M* for both trifluoroacetic and trichloroacetic acid the H_0 and H_- scales diverge and at concentrations of about 6 *M* the H_- scales indicate acidities of from 0.5 to 1 unit above those for the H_0 scales. Incidentally, the direction of this divergence as well as of that noted by Bates and Schwarzenbach (5) is nicely consistent with the "salting-in" discussion of Section III,D, since salting in of the uncharged form of the indicator will cause a decrease in the H_0 acidity but an increase in the H_- acidity.

At least one set of measurements has been made of H_+, that of Brand, Horning, and Thornley (12) for solutions of sulfur trioxide in sulfuric acid. The indicator was *m*-nitroanilinium ion. For this case H_+ was found to parallel H_0, and from approximate calculations the investigators conclude that for these sulfuric acid solutions the H_+ scale is about 0.3 unit more negative than H_0.

B. The J_0 acidity function for secondary base indicators

A distinctly different acidity function was proposed by Westheimer and Kharasch (99) and has been further developed by several other investigators. This function is designed to provide an acidity scale for secondary bases, those that react (i.e., "ionize") according to the equation:

$$\mathrm{ROH} + \mathrm{H}^+ \rightarrow \mathrm{R}^+ + \mathrm{H_2O}$$

where R^+ is a carbonium ion. The initial studies were with the indicator 4,4′,4″-trinitrotriphenylcarbinol in 80–95 per cent aqueous sulfuric acid. That compounds of this type actually react with acids in the manner indicated has been established by cryoscopic studies in 100 per cent sulfuric acid (75). The usefulness of the new acidity function was early evident from the fact that the behavior of this indicator closely paralleled the rate of nitration of nitrobenzene and other compounds, whereas the H_0 acidity function did not (66, 99).

By analogy to H_0, an obvious way to define the new acidity function (for uncharged secondary bases) is by means of the equation:[11]

$$J_0 \equiv -\mathrm{p}K_{\mathrm{ROH}} - \log \frac{C_{\mathrm{R}^+}}{C_{\mathrm{ROH}}} \tag{14}$$

where K_{ROH} represents an equilibrium constant for the above reaction. An equation of this form has in fact been suggested by all of the recent investigators. It is formally equivalent to:

$$J_0 = -\log \frac{a_{\mathrm{H}^+} f_{\mathrm{ROH}}}{a_{\mathrm{H_2O}} f_{\mathrm{R}^+}} \tag{15}$$

where activity coefficients refer to molar-concentration units and approach unity at infinite dilution in water, but (as is conventional) $a_{\mathrm{H_2O}}$ refers to mole-fraction units and itself reduces to unity for pure water. When so defined, J_0 (like H_0) approaches pH in dilute aqueous solutions.

As with the acidity functions previously described, the important problems are to determine the generality of the function and to obtain usable values of it. Lowen, Murray, and Williams (66, 74), who made the first extensive measurements with indicators, showed that such a function probably existed for solutions of from 65 to 90 per cent sulfuric acid in water in that the slopes of the ionization curves, log $(C_{\mathrm{R}^+}/C_{\mathrm{ROH}})$ vs. acid concentration, were essentially parallel for the several indicators tested. They also noted that their data sufficed to give a relative acidity scale over this range but not an absolute one.

All but one of the indicators used by Lowen, Murray, and Williams were in fact ionic carbinols (arylammonium derivatives) bearing two or three positive charge units. The exception was 4,4',4''-trinitrotriphenylcarbinol, the same indicator used by Westheimer and Kharasch. The observation that the slope of the ionization curve for this indicator was very close to the slopes for the charged carbinols suggests that at least for concentrated solutions of sulfuric acid the charged carbinols are satisfactory J_0 indicators.

A relationship between J_0 and H_0 may be derived by substituting equation 2 in equation 15:

$$J_0 = H_0 + \log a_{\mathrm{H_2O}} - \log \frac{f_{\mathrm{BH}^+} f_{\mathrm{ROH}}}{f_{\mathrm{B}} f_{\mathrm{R}^+}} \tag{16}$$

Gold and Hawes (32) suggested that absolute values of J_0 could be obtained from those of H_0 by the approximation

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[11] Of the symbols (H_{R}, J_0, and C_0) so far suggested by various investigators for this acidity function, the authors have adopted J_0 simply because of serious reservations about the practicality of the other two. H_{R} is too similar to the H functions of Hammett and coworkers; C_0 involves a symbol which is commonly used for concentration and which in any case has been overworked.

$$J_0' = H_0 + \log a_{H_2O}$$

i.e., by assuming that the last term in equation 16 might cancel out. Further indicator studies by Williams and Bevan (100) have shown, however, that this approximation is unsatisfactory at the lower acid concentrations, although it does appear to be useful for relative J_0 values in solutions containing more than 75 per cent sulfuric acid. Gold (30, 31) has recently proposed other more satisfactory approximations for the J_0 function.

Brand and Horning (11) have suggested that a J acidity function for fuming sulfuric acid (analogous to J_0 for water–sulfuric acid) can be determined from the relation $J = H_0 - \log p_{SO_3}$, where p_{SO_3} is the partial pressure of sulfur trioxide over the solvent. These authors use this to tabulate relative J values for sulfuric acid containing from 5 to 41 per cent of sulfur trioxide. There is as yet no evidence that this quantity is at all closely related to J_0, and it will be of considerable interest to investigate this medium with appropriate indicators.

The most extensive experimental study of secondary base indicators and of the generality of the J_0 acidity function has been made by Deno, Jaruzelski, and Schriesheim (22, 23, 24). These investigators determined pK_{ROH} values for a series of eighteen indicators by the overlapping-range technique discussed previously for H_0 indicators. The resulting values extend from $pK_{ROH} = -0.82$ (for 4,4′,4″-trimethoxytriphenylcarbinol) to +17.38 (for 2,4,6-trimethylbenzyl alcohol). These suffice to establish the J_0 scale for sulfuric acid–water mixtures of from 1 to 92 per cent acid. Since above about 82 per cent acid the last term in equation 16 appears to have a constant (though not zero) value determinable by comparison of J_0 with H_0, this equation may be used to extend the J_0 scale up to 98 per cent sulfuric acid from known values of H_0 and a_{H_2O}. Deno and coworkers showed that in analogy to figure 1, the slopes of the log (C_{R^+}/C_{ROH}) vs. acid concentration curves for adjacent indicators were very similar, suggesting that the J_0 function so defined is reasonably independent of the choice of indicator. This was confirmed by studies with ten additional aryl methanols.

Actually a minor difficulty appears to remain. Deno and coworkers made studies with the indicator 4,4′,4″-trinitrotriphenylcarbinol and report a slope, d log (C_{R^+}/C_{ROH})/d(% H_2SO_4), which is considerably smaller than that given

TABLE 9

The J_0 acidity function for sulfuric acid–water at 25°C. (23)

H_2SO_4	J_0	H_2SO_4	J_0	H_2SO_4	J_0	H_2SO_4	J_0
per cent		*per cent*		*per cent*		*per cent*	
0.5	1.25	15	−1.32	40	−4.80	70	−11.52
1.0	0.92	20	−1.92	45	−5.65	80	−14.12
2.0	0.62	25	−2.55	50	−6.60	90	−16.72
5.0	−0.07	30	−3.22	56	−7.90	95	−18.08
10	−0.72	35	−4.00	60	−8.92	98	−19.64

by the data both of Lowen, Murray, and Williams and of Westheimer and Kharasch for the same indicator in the same range of sulfuric acid concentrations. This may be due to slight variations in temperature or in indicator concentration, although the three studies appear to be quite similar on both counts.

Table 9 presents selected values of J_0 from the work of Deno, Jaruzelski, and Schriesheim (labeled C_0 in table 1 of reference 23). The striking feature is the rapid increase in acidity as measured by J_0 compared even with that measured by H_0. For example, $-H_0$ for sulfuric acid–water mixtures increases by 3.75 units between 60 and 90 per cent sulfuric acid, while $-J_0$ increases by 7.80 units over the same interval. Further studies on the generality of this function will be helpful, but since several investigators have already found correlations between J_0 and the rates of certain acid-catalyzed reactions, there is every reason to believe that this acidity function will be highly useful.

VI. MEASUREMENT OF STRENGTHS OF VERY WEAK BASES

A major field of application of the H_0 and other acidity functions is the study of equilibria involving acids and bases at high acidities, such as are encountered in the measurement of base strengths, solubilities, and distribution coefficients of very weak bases. Thus the establishment of an H_0 acidity scale in effect calibrates the medium for determining the pK_{BH^+} of other weak uncharged bases comparable in molecular size and structure to the indicator bases used to establish the scale. The extremely high acidities measurable on the H_0 scale without encountering serious experimental or theoretical difficulties admit significant measurements on extremely weak bases. The fact that many aromatic bases on ionization undergo color changes in the ultraviolet, if not in the visible portion of the spectrum, has been particularly helpful in the application of H_0 to this type of measurement.

Flexser, Hammett, and Dingwall (28) have developed specific methods for calculating values of pK_{BH^+} for weak bases from spectrophotometric measurements, particularly in concentrated aqueous sulfuric acid solutions. In principle the procedure is simple. The ratio of concentrations of ionized and uncharged forms is related to the extinction coefficients at a given wavelength by the equation:

$$\frac{C_{BH^+}}{C_B} = \frac{\epsilon_B - \epsilon}{\epsilon - \epsilon_{BH^+}}$$

where ϵ_B, ϵ_{BH^+}, and ϵ are the extinction coefficients of the uncharged base, the conjugate acid, and the test solution, respectively. Then, knowing H_0 for the test solution:

$$pK_{BH^+} = H_0 + \log \frac{\epsilon_B - \epsilon}{\epsilon - \epsilon_{BH^+}} \tag{17}$$

The difficulty is that ϵ_B and ϵ_{BH^+} are not precisely known because of their dependence on the medium.

Two specific methods were proposed for minimizing the effects of the medium and obtaining accurate pK values. One was to solve equation 17 by least squares for several wavelengths so chosen that either the ϵ_B or the ϵ_{BH^+} absorption curve was flat to minimize medium effects on its determination; that is, the extinction coefficient of the conjugate form was treated as an unknown together with pK_{BH^+}. The other method utilized the assumption that medium effects involve mainly lateral spectral shifts and that a true isobestic point could be found for absorption curves close to the 50 per cent ionization region; the medium effect could then be minimized by shifting all other curves laterally until they intersected at the common isobestic point, thus permitting the determination of corrected values of ϵ_B and ϵ_{BH^+}. Davis and Geissman (19) have recently reported another quite simple procedure for minimizing medium effects; a graphical method is used to determine the point of 50 per cent ionization and hence the point at which p$K_{BH^+} = H_0$.

For a colorless base or for one that undergoes only a slight spectral change with ionization, one may determine pK_{BH^+} by observing its effect on H_0 as measured by an indicator also present in the test solution. By this means the base strengths of some relatively weak bases have been measured in solutions of benzenesulfonic acid in anhydrous formic acid (47) and in solutions of perchloric acid in anhydrous acetic acid (61).

Table 10 gives pK_{BH^+} values for selected weak bases whose strengths have been determined by their ionization in solutions of known H_0. In such determina-

TABLE 10

Strengths, pK_{BH^+}, *of selected weak bases from ionization at approximately 25°C. in solutions of known* H_0

Values referred to pK_{BH^+} = 0.99 for *p*-nitroaniline

Base	pK_{BH^+}	References
Benzoic acid	−7.38	(28, 50)
Phenylacetic acid	−7.71	(28)
Acetophenone	−6.15	(28)
p-Methylacetophenone	−5.47	(27)
p-Bromoacetophenone	−6.52	(27)
Propiophenone	−6.40	(101)
n-Butyrophenone	−6.33	(101)
Isobutyrophenone	−6.84	(101)
Flavone	−1.3	(19)
2′,4′,6′-Trimethylflavone	−2.17	(19)
2,4,6-Trimethylbenzaldehyde	−4.7	(89)
2,4,6-Triethylbenzaldehyde	−5.0	(89)
2,4,6-Triisopropylbenzaldehyde	−5.2	(89)
2,4,6-Trimethylacetophenone	−7.9	(88)
2,4,6-Trimethylbenzoic acid	−7.4	(87)
p-Nitrophenol	−9.18	(33)
p-Fluoronitrobenzene	−11.62	(12)
p-Chloronitrobenzene	−11.68	(12)
m-Chloronitrobenzene	−12.27	(12)
m-Nitrotoluene	−10.96	(12)
Acetonitrile	−4.3	(61)
Propionitrile	−4.31	(47)
Dioxane	−4.4	(61)
Urea	+0.4	(61)
Acetamide	+0.25	(34)
Acetylglycine	−2.04	(34)
Acetic acid	−6.2	(34)

tions it is essential that equation 7, on which the validity of the H_0 function depends, be satisfied. One may always test this condition by observing how closely the ionization curve for the base remains parallel with changing acidity to those of the standard indicators. However, for solutions in solvents of low dielectric constant this condition may not be sufficient, as is evident from the observed displacement in figure 10 of the curve for 2,4-dichloro-6-nitroaniline in anhydrous acetic acid. The possibility of this type of difficulty casts doubt on the validity of pK values reported from measurements in such solvents.

Hammett and Chapman (45) have investigated the solubilities of benzoic acid and other very weak oxonium bases in sulfuric acid–water mixtures. These compounds show a striking increase in solubility as the sulfuric acid concentration is increased beyond 60 per cent by weight. Although conversion to the soluble conjugate acid is doubtless an important contributing factor, these investigators showed that it is not the only one responsible. Solubility equilibrium involves specifically the activity coefficient, f_B, which with increasing concentration of dissolved B (and BH^+) is by no means a function simply of the acidity of the medium. A similar consideration applies to the distribution of a weak base between an acid and a nonionizing medium, as in the study of substituted azulene bases by Plattner, Heilbronner, and Weber (81). In studies of this kind involving a second phase, independent knowledge of H_0 and of pK_{BH^+} may prove to be a valuable asset, but acid–base equilibrium in the one phase is itself not determinative.

A rather different kind of application of H_0 indicators is to the determination of the acid strength of solid surfaces. Walling (98b) has proposed that if an adsorbed indicator can go from the uncharged basic form to the acid form in the usual way by accepting a proton from the surface, then observation of the colors respectively assumed by a series of adsorbed indicators permits one to assign to the surface an H_0 value identical in significance with that defined by equation 2, all activities and activity coefficients referring to constituents in the adsorbed layer. The generality of this application of the H_0 scale may be tested by the consistency of the results obtained with different indicators. If, on the other hand, the surface functions as a Lewis acid, then the apparent H_0 value will have a rather different meaning, for the indicator equilibria will then be specific to the particular acid or electron acceptor active in the surface. Using indicators adsorbed from solutions in isoöctane (98b) and in benzene (9a), surface acidities have been determined for a number of common chemical solids (including titanium dioxide, cuprous chloride, silver chloride, tungstic acid) and also for several surface-active catalysts (silica gel, alumina, clay catalysts). Some of these turn out to have astonishingly high acidities. A synthetic silica–alumina cracking catalyst, for example, will convert adsorbed anthraquinone ($pK_{BH^+} = -8.27$) to its yellow acid form (9a).

VII. SUMMARY

The acidity function H_0 is defined by the equation

$$H_0 = pK_{BH^+} - \log (C_{BH^+}/C_B)$$

which is equivalent to

$$H_0 = -\log (a_{H^+}f_B/f_{BH^+})$$

It is determined by measurement of the indicator ratio C_{BH^+}/C_B for an uncharged indicator base B and of the thermodynamic ionization constant K_{BH^+} for its conjugate acid. The reference state is water, and H_0 is designed to become equal to pH and hence to $-\log C_{H^+}$ for dilute aqueous solutions.

The H_0 function is well established for aqueous solutions. Values of the function are tabulated for aqueous solutions of the mineral acids up to 10 *M* concentration (7 *M* for nitric acid) and for sulfuric acid–water mixtures to 107 per cent sulfuric acid (31 per cent sulfur trioxide in sulfuric acid). The H_0 values are calculated using "best values" of pK_{BH^+} for the indicators, referred to $pK_{BH^+} = 0.99$ for *p*-nitroaniline. Some studies have been made of the effect of neutral salts on the magnitude of H_0, and it is found that the results depend both on the specific salt and on the indicator used. A few studies are available on H_0 values for aqueous solutions of weak acids, but it is not yet known whether the H_0 scale for this type of solution is adequately independent of the choice of indicator.

Values of H_0 can be determined for solutions in mixed and in nonaqueous solvents. For any new solvent it is important to establish whether an H_0 function of some generality actually exists. Data are available for solutions of acids in such solvents as formic acid, acetic acid, ethanol, dioxane, acetone, and mixtures of the last four with water, but in almost every case it would be helpful to make studies with additional indicators to ascertain the generality of the H_0 function.

Studies have been made on the related acidity function H_- (where the indicator bases carry unit negative charge) with such solvents as aqueous alkali and aqueous hydrazine. Some comparisons are available of H_- and H_0, as well as of H_0 and H_+. A rather different type of acidity function called J_0 has been defined for the ionization of secondary bases

$$\mathrm{ROH} + \mathrm{H}^+ = \mathrm{R}^+ + \mathrm{H_2O}$$

and values of J_0 are available for mixtures of sulfuric acid and water.

The establishment of indicator acidity scales permits the measurement of p*K* values for bases of the same type as the indicator. The procedure is simple in principle, although slightly complicated by effects of the medium. A number of p*K* values for very weak uncharged bases are available from applications of the H_0 function. Similar but less extensive studies have been made with the H_- and J_0 functions.

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RECENT ADVANCES IN ISOCYANATE CHEMISTRY[1]

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I. INTRODUCTION

Significant industrial progress in isocyanate chemistry has occurred only within the past twenty years despite the fact that numerous references to both synthesis and reactions are to be found in the literature (241). Greatest progress has been made in the fields of polymers and polymer modification (96). Technological effort was stimulated by the development of diisocyanates, which are peculiarly adapted to polymer synthesis as a consequence of their reactivity.

A review of the synthesis and general reactions of isocyanates was published in 1948 (184). The purpose of this résumé is to extend this review to include not only the numerous contributions published since its preparation but also some new contributions from our laboratories.

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[1] Contribution No. 207 from the Jackson Laboratory. Excerpts from this paper were presented by R. G. Arnold before the Division of Rubber Chemistry at the 129th Meeting of the American Chemical Society, Cleveland, Ohio, May 16, 1956.

II. SYNTHESIS

Several new mono- and polyisocyanates are described in the current literature (25, 26, 38, 97), and numerous patents have been issued (28, 29, 42, 109, 110, 122, 130, 149, 153, 154, 169, 179, 202, 218, 219). Although recent developments have provided a large selection of isocyanates of unique structure, the synthetic methods are basically the same as those described in earlier reviews (184, 207). The preparative methods of greatest utility involve

(a) the phosgenation of amines (72, 73, 121, 122, 141, 153),
(b) the decomposition of acid azides (214),
(c) the dehydration of hydroxamic acids (242),
(d) the double decomposition reaction between a cyanate salt and an ester of an inorganic acid (26, 241), and
(e) the thermal decomposition of ureas (25, 171, 221) and urethans (27a, 27b, 50, 207).

Three new classes of isocyanates have been developed in recent years. Among these are (*a*) organophosphorus isocyanates (2, 3, 97),

$$RPOCl_2 + 2AgOCN \xrightarrow[\sim 80°C.]{solvent} RPO(NCO)_2 + 2AgCl$$

(*b*) fluorinated isocyanates,

$$CF_3COCl \rightarrow CF_3CONH_2 \rightarrow CF_3NCO \quad (1)$$

$$C_nF_{2n+1}CH_2NH_2 + COCl_2 \xrightarrow{cold}$$

$$C_nF_{2n+1}CH_2NHCOCl \xrightarrow[excess\ COCl_2]{heat} C_nF_{2n+1}CH_2NCO \quad (179)$$

and (*c*) sulfonyl isocyanates (130):

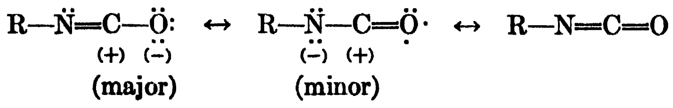
$$RSO_2NH_2 + COCl_2 \xrightarrow[\sim 160°C.]{solvent} RSO_2NCO + 2HCl$$

A new synthetic method utilizing *N*-haloformamides has been reported also (110).

$$HCONRX \xrightarrow{tertiary\ amine} RNCO + R_3N \cdot HX$$

III. REACTIONS OF ISOCYANATES

The reactions and reactivity of isocyanates can best be understood by considering the electronic structure of the isocyanate group and the effect on this structure of various groups attached to the nitrogen atom. A qualitative consideration of the resonance hybrids from the standpoint of the molecular orbital theory indicates that the electron or charge density is greatest on the oxygen (highest net negative charge) and least on the carbon (highest net positive charge), the nitrogen atom being intermediate with a net negative charge.



$$\underset{(major)}{R-\underset{(+)}{\ddot{N}}=C-\underset{(-)}{\ddot{O}}:} \leftrightarrow \underset{(minor)}{R-\underset{(-)}{\ddot{N}}-C\equiv\underset{(+)}{\dot{O}}\cdot} \leftrightarrow R-N=C=O$$

The reactions of isocyanates with active hydrogen compounds involve attack by a nucleophilic center upon the electrophilic carbon of the isocyanate. Therefore, if steric factors are neglected, any electron-withdrawing group attached to the NCO moiety will increase the positive charge on the carbon atom, thereby increasing the reactivity of the isocyanate towards nucleophilic attack. Conversely, electron-donating groups will reduce the reactivity of the NCO group, as illustrated below:

$$O_2NC_6H_4\text{—} > C_6H_5\text{—} > p\text{-}CH_3C_6H_4 > p\text{-}CH_3OC_6H_4\text{—} \gg C_6H_{11}\text{—} = C_nH_{2n+1}\text{-}$$

Likewise, the reactivity of the agent attacking the electrophilic carbon of the NCO group will increase as its nucleophilicity increases, as shown in the following series:

$$CH_3NH_2 > C_6H_5NH_2 > CH_3OH > C_6H_5OH > CH_3SH >$$

$$\underset{H}{\overset{\diagdown\ \diagup}{N}}$$

Consideration of the above factors in most cases makes it possible to predict on a qualitative basis the relative reactivity of various isocyanates with compounds containing active hydrogen. However, failure to consider steric factors, such as those encountered in ortho-substituted aromatic reactants, can lead to erroneous predictions.

An indication of the effect of steric hindrance on the rate of isocyanate–amine reactions is given in table 1 (47). The data indicate that a substituent ortho to the isocyanate function hinders the reaction more effectively than a substituent ortho to the amine function.

A. *Nitrogen–hydrogen bonds*

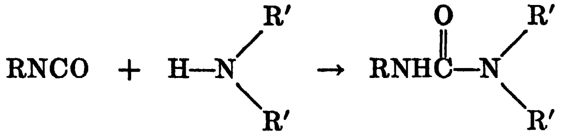
The reaction of isocyanates with compounds which contain nitrogen–hydrogen bonds is governed primarily by the basicity or nucleophilicity of the N—H bond.

TABLE 1

Effect of steric hindrance on the rate of isocyanate–amine reactions

(Amine, 0.1 *M*; isocyanate, 0.1 *M* in dioxane; 31°C)

Amine	$K_b \times 10^{-10}$	Isocyanate	Time to 50% Reaction
			minutes
Aniline. . . .	4.6	Phenyl	43
o-Toluidine.	3.3	Phenyl	60
Aniline	4.6	*p*-Tolyl	54
	4.6	*o*-Tolyl	202
o-Toluidine	3.3	*o*-Tolyl	>1000



$$RNCO + H{-}NR'_2 \rightarrow RNHC(=O){-}NR'_2$$

The effect of nuclear substituents on the reactivity of aryl isocyanates with arylamines has been reported (163). Isocyanate activity was found to decrease in the order

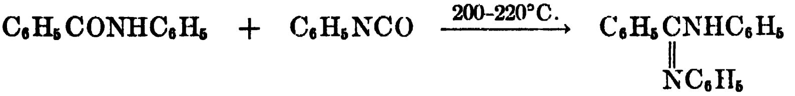
$$2,4\text{-}(NO_2)_2 > 3,5\text{-}(NO_2)_2 > 4\text{-}NO_2 > 3\text{-}NO_2 > 3\text{-}OCH_3 > H > 4\text{-}CH_3 > 4\text{-}OCH_3$$

whereas the amine activity increased in the same order. Pyridine and certain carboxylic acids were shown to be catalysts.

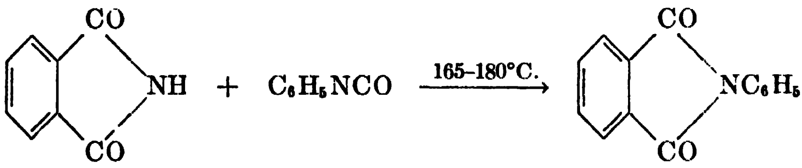
The relative reactivity of primary amines with phenyl isocyanate is shown in table 2. The data (51a) illustrate the greater reactivity of aliphatic amines.

Many other reactions involving the nitrogen–hydrogen bond are reported in the literature (184). In general the expected reactions occur, that is, the formation of a substituted urea. However, a number of anomalous reactions have been reported in the case of the following substances: (*a*) *N*-substituted amides under severe reaction conditions (231, 232),

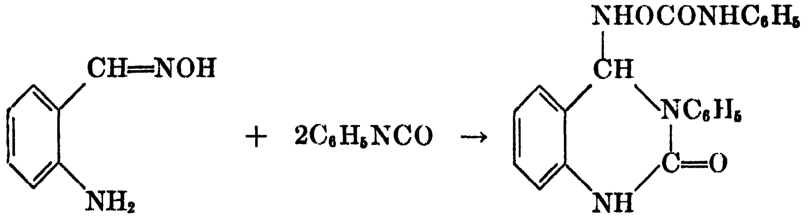
$$C_6H_5CONHCH_3 + C_6H_5NCO \xrightarrow{120°C.} C_6H_5CONHC_6H_5$$



$$C_6H_5CONHC_6H_5 + C_6H_5NCO \xrightarrow{200\text{-}220°C.} C_6H_5C(=NC_6H_5)NHC_6H_5$$



(*b*) *N*-substituted sulfonamides, which do not react with isocyanates although the unsubstituted derivatives do (171); (*c*) *o*-aminobenzaldoxime which, with phenyl isocyanate, gives 2-keto-3-phenyl-4-(β-hydroxylamine carbanilide)-1,2,3,4-tetrahydroquinazoline



in contrast to the meta and para isomers, which give the expected dicarbanilino derivatives (91); and (*d*) phenyl isocyanate when reacting with liquid ammonia in the presence of potassium amide, a reaction which produces carbanilide as well as the expected *N*-phenylurea (230).

TABLE 2

Relative reactivity of amines with phenyl isocyanate

Amine	Relative Reactivity	Amine	Relative Reactivity	Amine	Relative Reactivity
Ammonia	1	Propylamine	8.22	Amylamine	9.17
Ethylamine	9.72	Butylamine	9.17	Aniline	0.53

B. Oxygen–hydrogen bonds

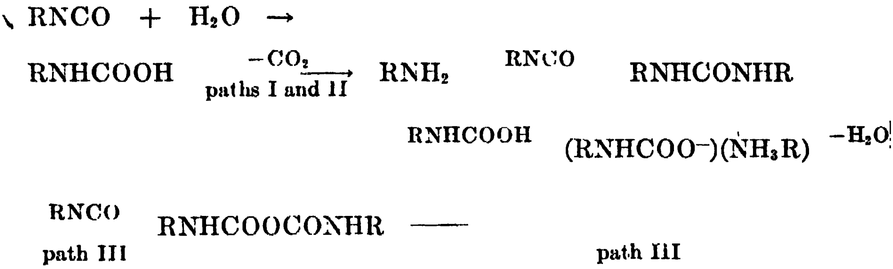
The reactions of isocyanates with compounds containing an oxygen–hydrogen bond represent one of the most important areas of isocyanate chemistry.

In general, they react rapidly with water at ordinary temperatures, giving rise to 1,3-disubstituted ureas and carbon dioxide (151):

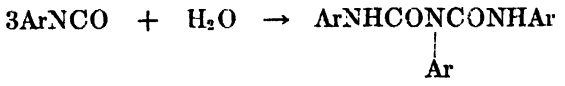
$$RNCO + H_2O \rightarrow RNHCONHR + CO_2$$

however, in the presence of sodium hydroxide the principal product is the primary amine.

The reaction of substituted aromatic isocyanates with water has been reported (163). On the basis of experimental evidence, three reaction paths for the formation of disubstituted ureas are proposed. The intermediate products formed by a particular isocyanate depend on the reaction conditions, the electronic structure, and the orientation of substituents on the aromatic nucleus. The influence of substituent groups (163) on the ability of aromatic isocyanates to form the free amine rather than the urea is given in table 3.



The direct synthesis of triarylbiurets by the reaction of aromatic isocyanates and water has been reported (92).



$$3ArNCO + H_2O \rightarrow ArNHCON(Ar)CONHAr$$

The mechanism of this reaction is not known beyond the fact that it does not involve the intermediate formation of the urea. Conditions which favor this "direct" biuret formation include an aromatic solvent such as benzene or the isocyanate itself at 60–90°C. For example, in the case of phenyl isocyanate, triphenylbiuret is obtained in 1 hr. with only 2 per cent of carbanilide being formed. The reaction between phenyl isocyanate and carbanilide, even in the presence of water, is much too slow at 90°C. to account for this high conversion to the biuret.

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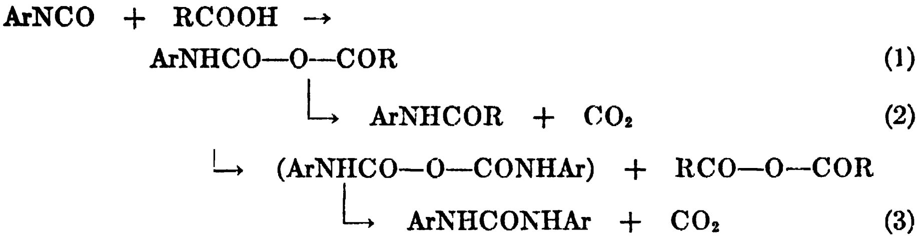
TABLE 3

Influence of substituent groups on the ability of isocyanates to form the free amine rather than the urea in reaction with water

R in RNCO	Product	R in RNCO	Product
2,4,6-Trinitrophenyl	Amine	3-Nitrophenyl	Amine + urea
2,4-Dinitrophenyl	Amine	3-Methoxyphenyl	Urea
2-Nitrophenyl	Amine + urea	Phenyl	Urea
3,5-Dinitrophenyl	Amine + urea	4-Methylphenyl	Urea
4-Nitrophenyl	Amine + urea	4-Methoxyphenyl	Urea

Alcohols and phenols react with isocyanates to yield carbamate esters (184). These derivatives are often used for the characterization of hydroxyl-containing compounds (87).

Weak aromatic and aliphatic carboxylic acids readily form mixed anhydrides with isocyanates (reaction 1), whereas stronger acids such as cyanoacetic, trichloroacetic, and formic acid form mixed anhydrides which spontaneously decompose into amides and carbon dioxide (reaction 2). The more stable mixed anhydrides decompose at elevated temperatures into disubstituted ureas, carboxylic acid anhydrides, and carbon dioxide (reaction 3) (161, 162, 171, 184).



$$\mathrm{ArNCO} + \mathrm{RCOOH} \rightarrow$$

$$\mathrm{ArNHCO{-}O{-}COR} \qquad (1)$$

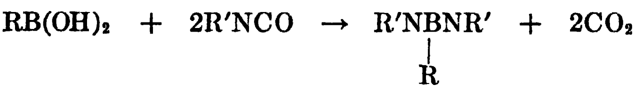
$$\hookrightarrow \mathrm{ArNHCOR} + \mathrm{CO_2} \qquad (2)$$

$$\hookrightarrow (\mathrm{ArNHCO{-}O{-}CONHAr}) + \mathrm{RCO{-}O{-}COR}$$

$$\hookrightarrow \mathrm{ArNHCONHAr} + \mathrm{CO_2} \qquad (3)$$

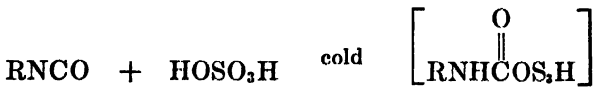
The decomposition of the mixed anhydride indicated in reaction 2 has been shown (86) to occur unequivocally by loss of the carbonyl function of the isocyanate as carbon dioxide (128).

The reaction of a boronic acid and an isocyanate results in the formation of a boronamide and carbon dioxide (226).



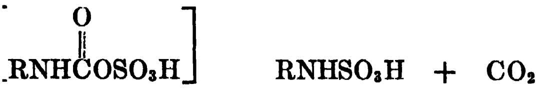
$$\mathrm{RB(OH)_2} + 2\mathrm{R'NCO} \rightarrow \mathrm{R'N}\underset{\displaystyle \mathrm{R}}{\underset{|}{\mathrm{B}}}\mathrm{NR'} + 2\mathrm{CO_2}$$

Sulfuric acid reacts with isocyanates in a manner similar to that described for carboxylic acids (27), in that the first step involves the formation of an unstable mixed anhydride.



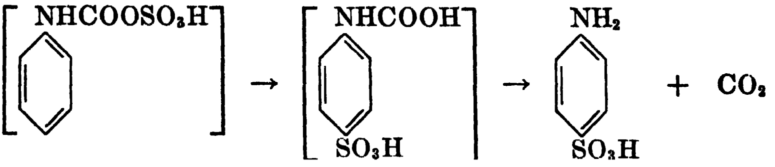
$$\mathrm{RNCO} + \mathrm{HOSO_3H} \quad \text{cold} \quad \left[\mathrm{RNH}\overset{\displaystyle \mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{OS_3H}\right]$$

With an alkyl isocyanate the mixed anhydride decomposes to a sulfamic acid and carbon dioxide.



$$\left.\mathrm{RNH}\overset{\displaystyle \mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{OSO_3H}\right] \qquad \mathrm{RNHSO_3H} + \mathrm{CO_2}$$

In the case of phenyl isocyanate, on the other hand, the product is sulfanilic acid, which is probably formed by the route shown below.



It appears that the reaction is essentially a sulfonation of the aromatic ring by the mixed anhydride and that *N*-phenylsulfamic acid is not an intermediate in the process, since, at low temperatures, *N*-phenylsulfamic acid rearranges to orthanilic acid and not to the para derivative.

C. Carbon–hydrogen bonds

N-Substituted amides are formed as a result of nucleophilic attack on isocyanates by the carbanions of sodiomalonic esters and related compounds (184). The nucleophilic α-position of pyrrole (225) or the methylene group of *N*-alkyl-2-methylenedihydropyridine (195) and related compounds (45, 150) undergoes similar reactions.

N-Substituted aroylamides are also produced by the Friedel–Crafts synthesis (93). An intramolecular carbamoylation occurs when 1-naphthyl isocyanates are fused with mixtures of aluminum and sodium chlorides, yielding naphthostyrils (55). The fusion of phenyl isocyanates or the corresponding dimers under similar conditions yields 3-phenyl-2,4-dioxotetrahydroquinazolines (54). Treatment of α-butylphenethyl isocyanates with aluminum chloride in an inert solvent yields 3-butyl-3,4-dihydro-1(2*H*)-isoquinoline (5).

D. Sulfur–hydrogen bonds

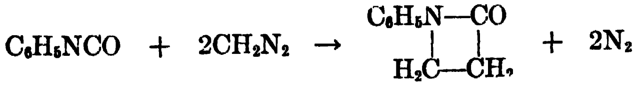
The thiol group reacts with isocyanates in the same way as its oxygen analog, except that it is very much less reactive (171). Hydrogen sulfide reacts with isocyanates to give disubstituted ureas and carbon oxysulfide (171).

E. Miscellaneous

Lithium aluminum hydride reduces aryl and alkyl isocyanates to the corresponding methylamines in high yield (85, 180, 299).

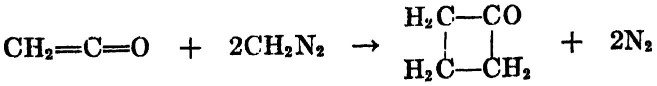
Most Grignard reagents and organometallics react smoothly and rapidly with isocyanates, forming *N*-substituted amides (125).

Diazomethane and phenyl isocyanate combine to yield the β-lactam, 1-phenyl-2-azetidinone (206).



$$C_6H_5NCO + 2CH_2N_2 \rightarrow \begin{array}{c} C_6H_5N\text{—}CO \\ |\quad\ \ | \\ H_2C\text{—}CH_2 \end{array} + 2N_2$$

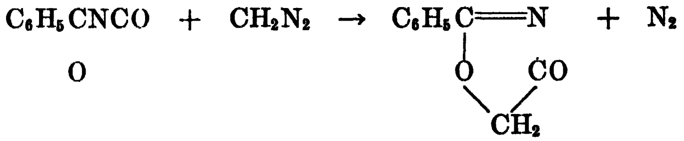
This reaction is analogous to that of ketene with diazomethane.



$$CH_2{=}C{=}O + 2CH_2N_2 \rightarrow \begin{array}{c} H_2C\text{—}CO \\ |\quad\ \ | \\ H_2C\text{—}CH_2 \end{array} + 2N_2$$

p-Bromophenyl isocyanate also yields the corresponding β-lactam with diazomethane, whereas α-naphthyl, *p*-nitrophenyl, benzyl, and benzoyl isocyanates do not form β-lactams.

Benzoyl isocyanate and diazomethane react to produce 2-phenyl-4-oxazolone in 70 per cent yield.

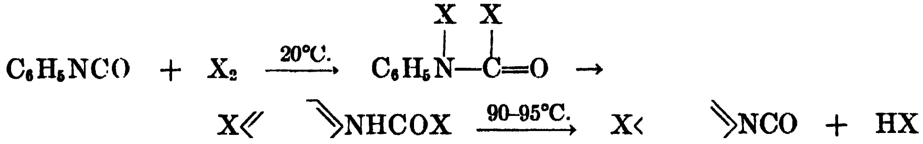


$$C_6H_5\underset{O}{C}NCO + CH_2N_2 \rightarrow C_6H_5C{=}N + N_2$$

Isocyanates give addition products with sodium bisulfite similar to those formed by aldehydes and ketones (171); in fact, isocyanates are capable of displacing the aldehyde or ketone from the sodium bisulfite adduct. Those from aliphatic isocyanates are more stable to hydrolysis, being capable of recrystallization from water, whereas the aromatic derivatives are sensitive to hydrolysis.

Dialkyl phosphites react with isocyanates to produce carbamoyl phosphonates (178).

Chlorine and bromine add to phenyl isocyanate, giving rise to a dihalide (94),



$$C_6H_5NCO + X_2 \xrightarrow{20°C.} C_6H_5\overset{X}{N}{-}\overset{X}{C}{=}O \rightarrow$$

$$X\langle\quad\rangle NHCOX \xrightarrow{90\text{-}95°C.} X\langle\quad\rangle NCO + HX$$

which may be rearranged to yield a mixture of the *o*- and *p*-halo-substituted aromatic isocyanates (89).

IV. POLYMERIZATION

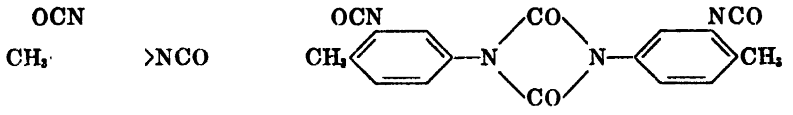
A. Dimers

The dimers of isocyanates are obtained by treatment of the monomer with catalysts. Triethylphosphine was used in the preparation of phenyl isocyanate

TABLE 4

Dimerization of toluene 2,4-diisocyanate (TDI) in benzene*

Catalyst, tributylphosphine



Starting Material	Temperature	Equilibrium Conversion
	°C.	*per cent*
Toluene 2,4-diisocyanate	25	74
Toluene 2,4-diisocyanate dimer	25	71
Toluene 2,4-diisocyanate	10	90

* Chemical Abstracts uses the name 4-methyl-*m*-phenylene diisocyanate for this compound.

dimer in 1858 (101, 102). Other alkyl- and arylalkylphosphines (13), pyridine (215), methyl-substituted pyridines (84), and triethylamine (142) are effective also. The dimer of phenyl isocyanate has been prepared also by the action of excess thionyl chloride on *N*-phenylurethan at room temperature (228),

$$\underset{N\text{-Phenylurethan}}{C_6H_5NHCOOC_2H_5} + 2SOCl_2 \rightarrow (C_6H_5NCO)_2 + 2C_2H_5Cl + 2SO_2 + 2HCl$$

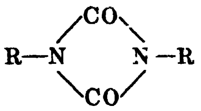
but this reaction appears to be limited to the phenyl derivative (175).

Aromatic isocyanate dimers are obtained readily and a large number have been reported, including some mixed dimers (see tables 5 and 6). Aliphatic isocyanates, in contrast, do not dimerize, although trimers have been made.

When pyridine is used as a catalyst for dimer formation, it is most conveniently applied as the solvent medium for the reaction (84, 215). Phosphine catalysts are much more active than pyridine and are used in trace amounts. A convenient method of controlling phosphine-catalyzed dimerizations has been described (13). It involves the addition to the reaction mass of an alkylating agent such as benzyl chloride in an amount stoichiometrically equivalent to the substituted phosphine present. Complete deactivation of the catalyst results. By this means the reaction may be mitigated or even quenched and then activated by the addition of more catalyst. The reaction product of the alkylating

TABLE 5

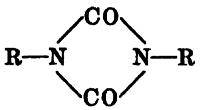
Monoisocyanate dimers

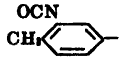
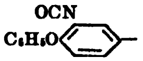
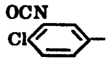
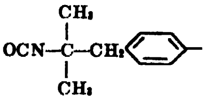
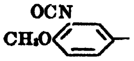


	Melting Point	References
	°C.	
Phenyl	175	(102, 176, 215)
m-Tolyl	159-160	(176)
p-Tolyl	185	(176)
p-Ethoxyphenyl	181–182	(176)
2-Chlorophenyl	234-235	(176)
3-Chlorophenyl	153–154	(176)
4-Chlorophenyl	155–156	(176)
4-Bromophenyl	203–204	(176)
4-Nitrophenyl	208–211	(176)
4-Aminophenyl	—	(136)
4-Amino-3-methylphenyl	—	(136)
3-Amino-4-methoxyphenyl	—	(136)
3-Amino-5-chlorophenyl	—	(136)
4-Phenylazophenyl	270 (dec.)	(176)
4-(4′-Aminophenyl)phenyl	281–282 (dec.)	(176)
3-Bromo-2-hydroxy-5-methylphenyl	—	(177)
1-Naphthyl	Sublimed at 296	(176)
2-Naphthyl	196–197	(176)
4-Amino-1-naphthyl	—	(136)
Mixed dimer of 4-chlorophenyl and 4-tolyl isocyanates	195	(176)

TABLE 6

Diisocyanate dimers



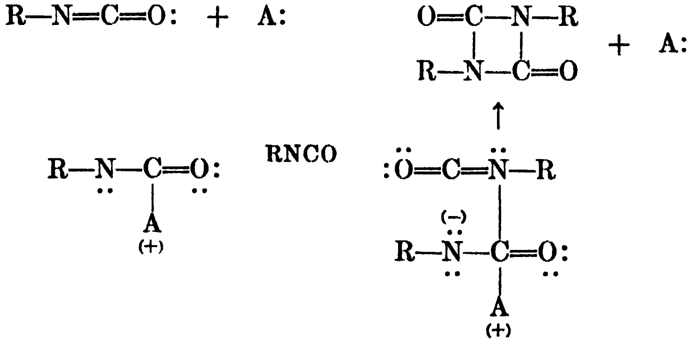
R	Melting Point	References	R	Melting Point	References
	°C.			°C.	
	156	(17, 84, 136)		179-181	(123)
	172-174	(12, 88)		168-169	(12)
	197	(123)			

agent and the phosphine catalyst (probably a phosphonium salt) does not interfere with the dimerization process. Finally, when the conversion is complete, the reaction mass may be stabilized and effectively freed of catalyst traces by treatment with the alkylating agent.

Among the phosphine catalysts the trialkyl derivatives are the most active. Dialkyl-aryl compounds, of which dimethylphenylphosphine is a good example, are more convenient in practice, however, because their action is more moderate, permitting better control of the exothermic dimerization reaction. When the phosphorus atom carries two phenyl groups, its efficiency as a catalyst is reduced, and triphenylphosphine exhibits no catalytic activity.

Isocyanate dimerization is an equilibrium reaction. The conversion to dimer increases with decreasing temperature, as illustrated (12) in table 4.

The known dimerization catalysts may all be described as nucleophilic agents. It is probable that dimerization occurs by the mechanism shown below:

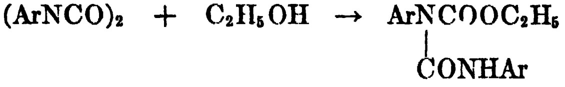


The availability of a pair of unshared electrons on the catalyst is not in itself sufficient, however. Obviously, structural or other factors must be involved. For example, dimethylphenylphosphine and dimethylaniline are about equal in base strength (50 per cent ethanol), but the phosphine is an extremely active catalyst and the amine is completely inactive.

The dissociation of isocyanate dimers occurs only at elevated temperatures. The dimer of toluene 2,4-diisocyanate is almost completely converted to monomer at 175°C. and has been reported to dissociate at 150°C. (17). It has been shown that dimer dissociation follows first-order kinetics, as would be expected (212).

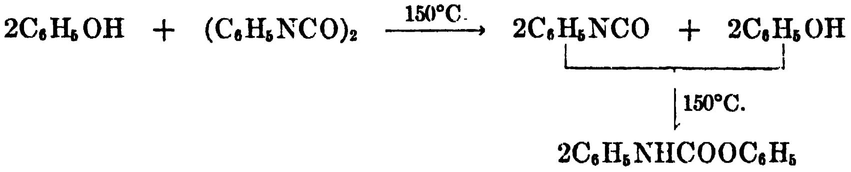
It has already been pointed out that the dimerization reaction involves an equilibrium. Thus, in solution in the presence of a phosphine catalyst dimers are dissociated even at low temperatures. For example, the dimer of toluene 2,4-diisocyanate is about 25 per cent dissociated at 25°C. in benzene solution and is 100 per cent dissociated at 80°C.

Alcohols react with isocyanate dimers to form allophanates (103).



$$(ArNCO)_2 + C_2H_5OH \rightarrow \underset{\displaystyle CONHAr}{ArNCOOC_2H_5}$$

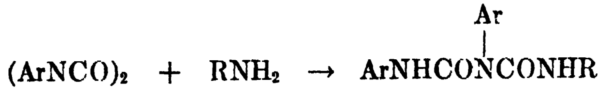
The reaction is slow, requiring prolonged heating of the dimer in alcohol. For this reason it is possible to employ ethanol as a solvent for the recrystallization of dimers. Phenol, at 100°C., does not react with phenyl isocyanate dimer (103) but a change does occur at 150°C.



$$2C_6H_5OH + (C_6H_5NCO)_2 \xrightarrow{150°C.} 2C_6H_5NCO + 2C_6H_5OH \xrightarrow{150°C.} 2C_6H_5NHCOOC_6H_5$$

Alcohols react with dimers in the presence of phosphine catalysts to yield the corresponding urethans, but this is probably the result of dissociation of the dimer to the free isocyanate rather than a direct attack on the dimer ring.

Amines combine with dimers to form biurets (103, 176).



$$(ArNCO)_2 + RNH_2 \rightarrow ArNHCO\overset{\displaystyle Ar}{N}CONHR$$

With ammonia or aliphatic amines the reaction is rapid (103, 183). Aromatic amines are less reactive and, in fact, there is some evidence that they will not react at all (below the dissociation temperature of the dimer, of course) unless a catalyst is present. Triphenylbiuret has been prepared from phenyl isocyanate dimer and aniline at 100°C., but there is evidence that the dimer was contaminated with triethylphosphine (103). Purified phenyl isocyanate dimer and

TABLE 7

Effect of various reagents on phenyl isocyanate dimer

Reagent	Product	Reagent	Product
Hydrogen chloride (dry)	No reaction	Chlorine	p,p'-Dichlorophenyl isocyanate dimer
H_2, copper chromite or Raney nickel, 125°C., 5000 p.s.i.	No reaction	Bromine	p-Bromophenyl isocyanate dimer
Acid potassium permanganate	No reaction	Nitric acid	p,p'-Dinitrophenyl isocyanate dimer
Glacial acetic acid	No reaction	Sulfuric acid (100%)	Sulfanilic acid

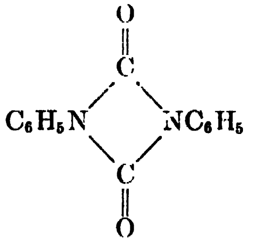
aniline do not react at 100°C.; in the presence of glacial acetic acid, however, a quantitative conversion to triphenylbiuret occurs at 25°C. within 3 hr. (124).

Ethylmagnesium bromide and methylmagnesium iodide react with phenyl isocyanate dimer to form carbanilide (176).

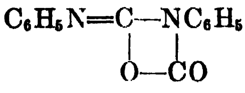
Aside from the reactions described above the dimer may be regarded as a relatively stable compound. For example, a number of nitrophenyl and nitronaphthyl isocyanate dimers have been catalytically reduced (palladium on charcoal) to the amino derivatives of the dimer, and these have been subsequently diazotized and coupled with suitable naphthols and phenols in aqueous medium (136). Table 7 lists a series of chemical reagents and their effect on phenyl isocyanate dimer.

B. Structure and nomenclature

A 1,3-diaryl-1,3-diazacyclobutane-2,4-dione structure has been postulated for aryl isocyanate dimers (220). This structure has generally been accepted and the current nomenclature is based upon it. In 1939 *Chemical Abstracts* (43) indexed isocyanate dimers as uretidiones. Subsequently this was changed to uretidine dione, a term which is currently in use. The compounds are still commonly referred to simply as isocyanate dimers. The original structure is supported by recent crystallographic work (33), which shows that the dimer of phenyl isocyanate possesses a center of symmetry and is isostructural with p-terphenyl (see formula I).

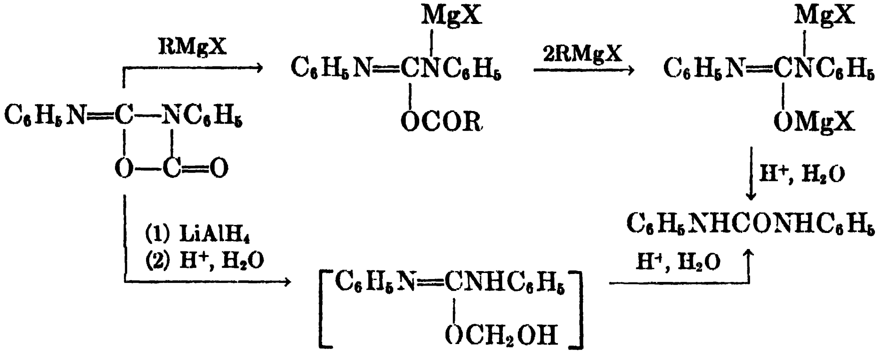


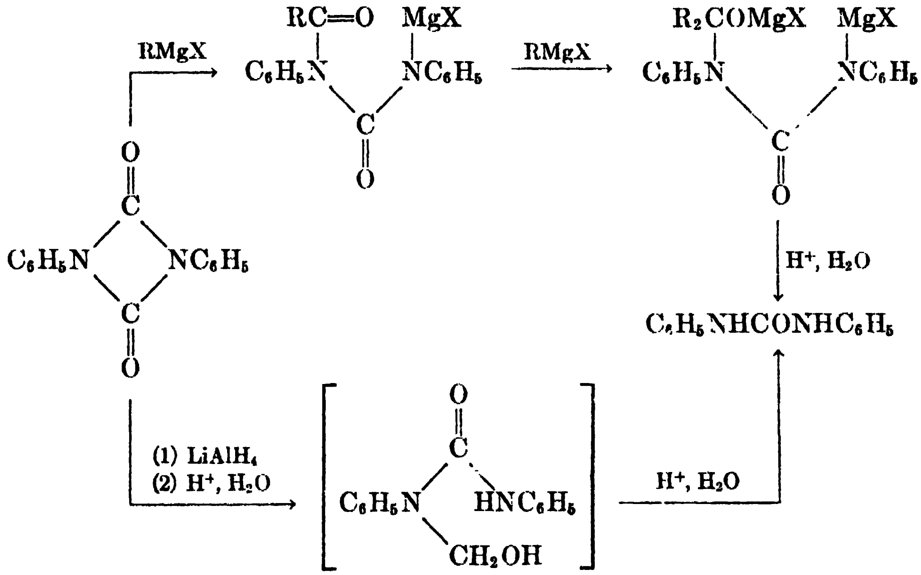
I



II

The isomeric structure (II) has been proposed recently on the basis of the reactions between phenyl isocyanate dimer and Grignard reagents or lithium aluminum hydride (86a). It appears reasonable, however, that both structures could yield the same final product, carbanilide, with these reagents, and the experiment is not yet definitive.





While crystallographic and infrared studies support structure I for the solid material, the possibility of rearrangements of the dimer in solution in the presence of reagents which may, secondarily, be catalysts cannot be ruled out.

C. Trimers

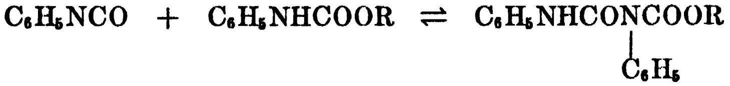
Both aromatic and aliphatic isocyanates form trimers (*N*-substituted isocyanurates) when treated with appropriate catalysts (184)

A new synthesis for aromatic isocyanate trimers has been reported (127). It is well known that, at moderate temperatures, the product of the reaction between an alcohol and an aromatic isocyanate is a carbanilate and that the reaction is catalyzed by tertiary amines (11). At elevated temperature (125°C.), however, in the presence of the amine catalyst a good yield of isocyanate trimer is obtained. The reaction follows the course shown below:

(*a*) Carbanilate formation:

$$C_6H_5NCO + ROH \rightarrow C_6H_5NHCOOR$$

(*b*) Allophanate formation:

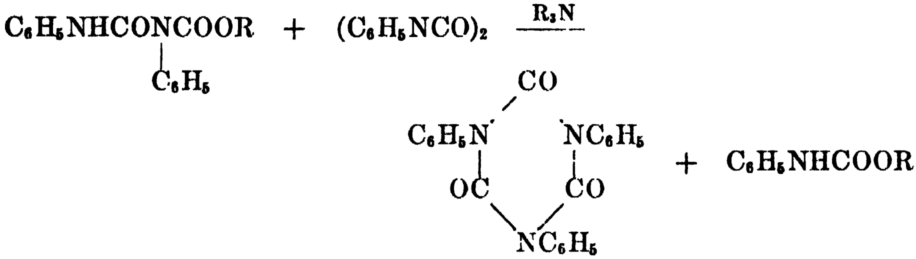


$$C_6H_5NCO + C_6H_5NHCOOR \rightleftharpoons C_6H_5NHCO\underset{\displaystyle C_6H_5}{\underset{|}{N}}COOR$$

(*c*) Isocyanate dimerization:

$$2C_6H_5NCO \xrightleftharpoons{R_3N} (C_6H_5NCO)_2$$

(*d*) Isocyanate trimerization:



Thus the actual trimerization results from the reaction of allophanate and dimer and only occurs in the presence of the tertiary amine catalyst. Two of the three moles of isocyanate required by the reaction are derived from the starting dimer, and the third is supplied by the allophanate. It is obvious from this example that the method can be employed for the preparation of unsymmetrical isocyanate trimers.

The infrared absorption spectra of aromatic isocyanate trimers exhibit differences depending upon the orientation of the substituents on the aromatic rings (127). Tri-ortho-substituted aryl isocyanurates show a single carbonyl absorption at 5.87-5.90 microns, whereas the tri-para-substituted compounds exhibit three absorption peaks associated with the carbonyl group. Typical data are presented in table 8.

TABLE 8

Infrared absorption spectra of some substituted phenyl isocyanate trimers

Substituent	Carbonyl Absorption Peak	Substituent	Carbonyl Absorption Peak
	microns		*microns*
H	5.90	p-CH_3	5.68, 5.86, 5.94
o-CH_3	5.90	p-Cl	5.66, 5.85, 5.95
o-Cl	5.88	p-OCH_3	5.70, 5.83, 5.95
o-NO_2	5.87	p-NO_2	5.67, 5.83, 5.94
o-OCH_3	5.87		

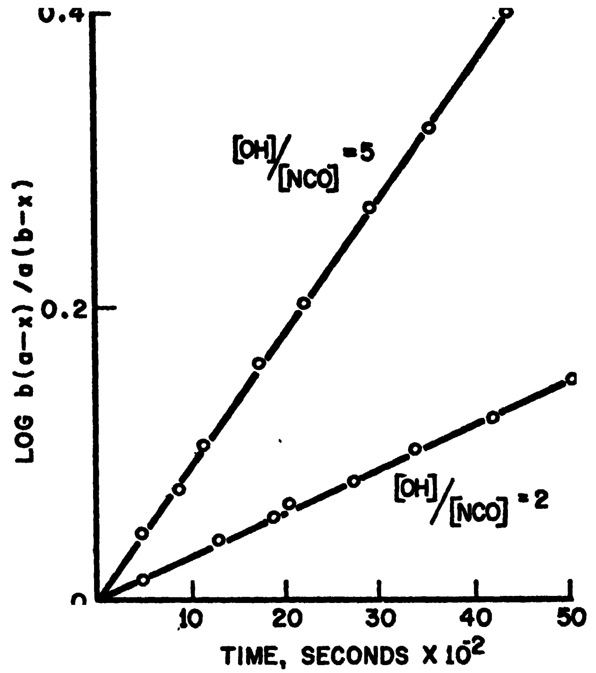
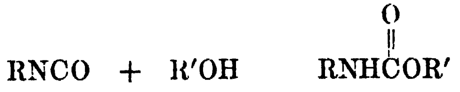


FIG. 1. Rate of reaction of *sec*-butyl alcohol with phenyl isocyanate in xylene at 25°C.

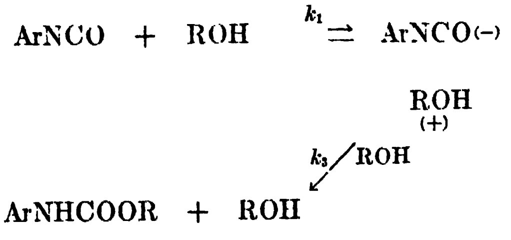
V. REACTION KINETICS

The stoichiometry of the reaction between an isocyanate and an alcohol is expressed by the simple equation:



$$\mathrm{RNCO} + \mathrm{R'OH} \qquad \mathrm{RNH\overset{\overset{O}{\|}}{C}OR'}$$

The kinetics of the reaction, however, are not as straightforward as this equation would indicate. The reaction appears to follow second-order kinetics, with the complication that the rate constant obtained is dependent upon the ratio of the alcohol–isocyanate concentrations, as figure 1 illustrates (59). This reaction has been studied extensively (7, 8, 9, 10, 11). The mechanism shown has been suggested to account for the experimental kinetic data.



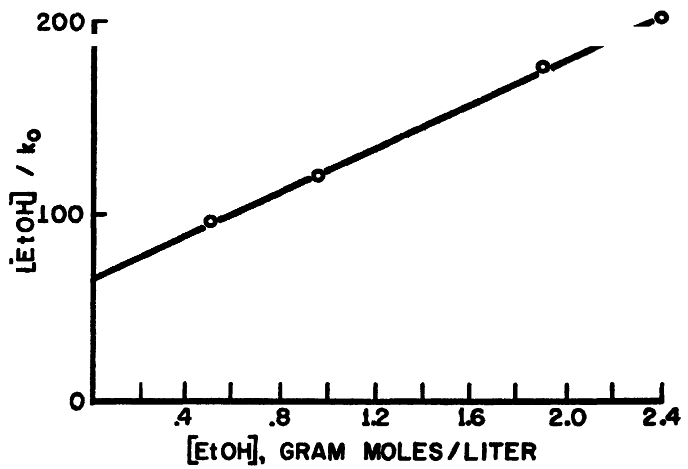


FIG. 2. Dependence of rate constant on alcohol concentration; reaction of ethyl alcohol with phenyl isocyanate in di-*n*-butyl ether at 20°C.

Using this mechanism the apparent second-order rate constant of the reaction, k_0, may be expressed as a function of the alcohol concentration:

$$k_0 = k_1k_3(\text{ROH})/(k_2 + k_3(\text{ROH}))$$

Rearranging:

$$(\text{ROH})/k_0 = k_2/k_1k_3 + (\text{ROH})/k_1$$

The straight line obtained by plotting $(\text{ROH})/k_0$ against (ROH) (figure 2) supports the correctness of the assumptions. This reaction has been examined in both di-*n*-butyl ether and benzene. Association and solvation play an important role in controlling the kinetics by virtue of the effect of these factors on the concentration of free alcohol in the solution. Because of such secondary effects perturbations were observed, but the assumptions as to the nature of the primary reaction appear sound.

From the foregoing it is obvious that the alcohol is playing a dual role as catalyst and reactant. Tertiary amines, with the exception of the *N*-dialkylanilines (7, 8, 9, 10), catalyze the reaction and are more effective in this role than alcohols. The second-order rate constant observed in an amine-catalyzed reaction is a linear function of the concentration of the tertiary amine.

$$k_0 = k_1k_3(\text{R}_3\text{N})/[k_2 + k_3(\text{R}_3\text{N})]$$

Rearranging:

$$(\text{R}_3\text{N})/k_0 = k_2/k_1k_3 + (\text{R}_3\text{N})k_1$$

Evidence adduced in the case of the alcohol–isocyanate reaction indicates that isocyanates are highly sensitive to the action of nucleophilic catalysts. Even the *N*-phenylurethan which is the product of the combination of phenylisocyanate with an alcohol is a weak catalyst for the reaction (11). Consequently,

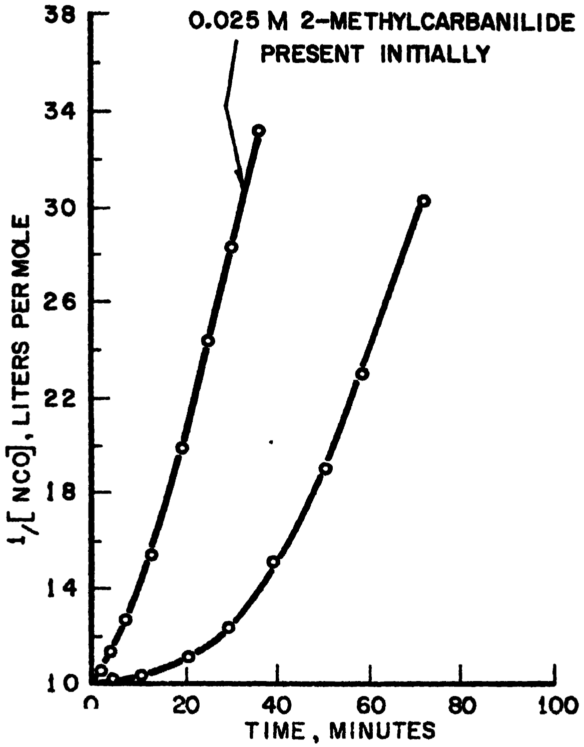


Fig. 3. Rate of reaction of 0.1 M phenyl isocyanate with 0.1 M *o*-toluidine in dioxane at 31°C.

it is to be expected generally that reactions involving other nucleophilic reagents, such as amines, water, mercaptans, and their nucleophilic reaction products, will exhibit anomalous kinetics rather than the simple second-order relationship suggested by the stoichiometric equations. That this expectation is well founded is illustrated by results obtained with phenyl isocyanate and *o*-toluidine, which combine to form 2-methylcarbanilide. The results shown in figure 3 demonstrate that the reaction is not simple second order and that it is strongly catalyzed by the urea which is the product of the reaction (47). The scheme which is illustrated is consistent with the kinetic data.

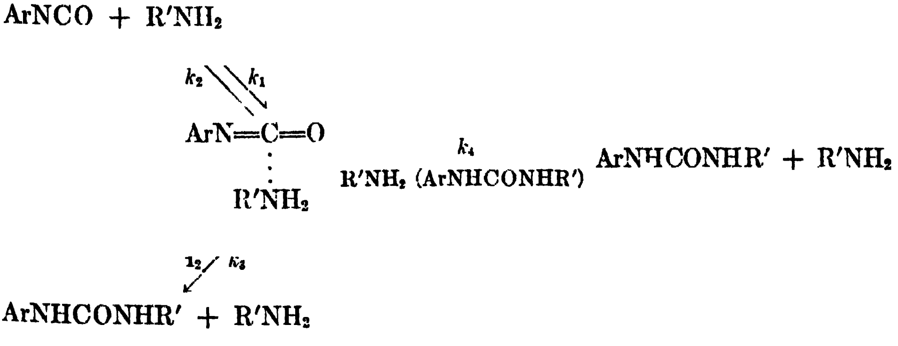


TABLE 9

Initial rates of amine–isocyanate reactions

$R_0 = k(\text{I})(\text{A})^n$

Amine	Isocyanate	n
p-Toluidine	Phenyl	∽1.0
Aniline	Phenyl	1.7
o-Toluidine	Phenyl	1.85

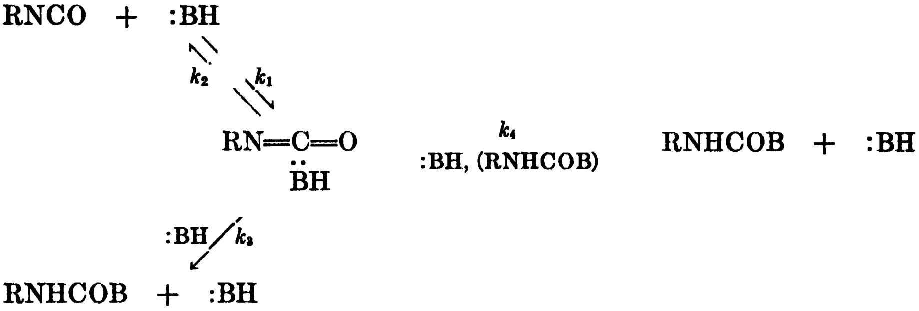
This sequence is identical in principle to that presented for the phenyl isocyanate–alcohol reaction. The differences between the amine and the alcohol reactions reside in the relative catalytic activity of the reactants and products. The carbanilide formed in the amine reaction is a much stronger catalyst for the reaction than is the urethan which is the product in the alcohol reaction. For this reason the kinetic expressions become more complicated, since they must include a term for the carbanilide concentration. Further, the amine itself is a more active catalyst than is alcohol. This is indicated by the fact that a tertiary amine accelerates the isocyanate–alcohol reaction and the apparent second-order rate constant becomes dependent upon the amine concentration, whereas a tertiary amine does not appreciably increase the rate of the isocyanate–amine reaction.

While the general principles described above apply to the kinetics of amine–isocyanate reactions, specific examples display considerable individuality. The initial rates of the reactions measured before appreciable quantities of product carbanilides have formed show substantial variations in their dependence upon the amine concentration, as illustrated in table 9. Furthermore, the catalytic activities of the product carbanilides show considerable variation. Development of the kinetic expressions on the basis of the same assumptions used for the alcohol–isocyanate reaction discussed above allows the assessment of the ratio of the specific rate constants k_3 and k_4 (see scheme for the amine–isocyanate reaction). The value of this ratio (k_3/k_4) provides an indication of the relative catalytic activity of the product carbanilides. The value of this ratio for the reaction between phenyl isocyanate and *o*-toluidine is 0.02; for phenyl isocyanate and aniline, 0.073; and for phenyl isocyanate and *p*-toluidine, 0.40. The apparent catalytic activity of the product carbanilides decreases in the same order.

The lack of catalytic activity of 4-methylcarbanilide in the reaction between *p*-toluidine and phenyl isocyanate may well be a consequence of the relatively high base strength of *p*-toluidine, which overpowers the weakly basic carbanilide in performing the catalytic function for the reaction. When *p*-tolyl isocyanate is reacted with aniline, the same product carbanilide is formed, but the overall reaction is slower and is weakly catalyzed by the reaction product.

The kinetics of the reaction between water and aryl isocyanate indicate that this reaction also follows the same general pattern outlined for the alcohols and amines (213). In other words, water is a catalyst for its own reaction with an isocyanate.

On the basis of the studies which have been outlined it is possible to generalize the reactions of aryl isocyanates with alcohols, amines, and water.



Kinetic investigations undertaken in the field will have to account for at least four specific rate constants to explain these superficially simple reactions.

It is apparent that rate constants for the reactions of isocyanates with nucleophilic reagents, where they can be determined, will be specific rather than general, each one qualified by the conditions of solvent and catalysis under which it was obtained. Nevertheless, kinetic experiments have supplied data which give more exact meaning to the comparisons of the reactivities of various types of isocyanates and attacking reagents. For example, in table 10 the effect of changing the electronegativity of the group attached to the nitrogen atom of the isocyanate function on the reactivity of that function toward methyl alcohol (11) is shown. These data emphasize the much greater reactivity of aromatic as compared to aliphatic isocyanates and the wide range of activity available within the family of isocyanates.

VI. DIISOCYANATES

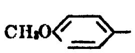
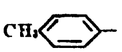
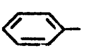
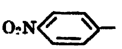
In the polymer field only di- and polyisocyanates are of interest. They are reactive building units capable, under the proper conditions, of forming high-molecular-weight materials. Application of di- and polyisocyanates has been extensive. The more reactive aromatic compounds are receiving the greatest attention.

The chemistry of isocyanates as defined by work with monoisocyanates is applicable with little or no modification. One feature of the transition, however, which has received some attention is the effect of one isocyanate function upon the reactivity of another when both are attached to the same aromatic nucleus. Rate studies performed on *o*- and *p*-tolyl isocyanate–amine systems (47) showed that *p*-tolyl isocyanate is the more reactive and one would be justified in suspect-

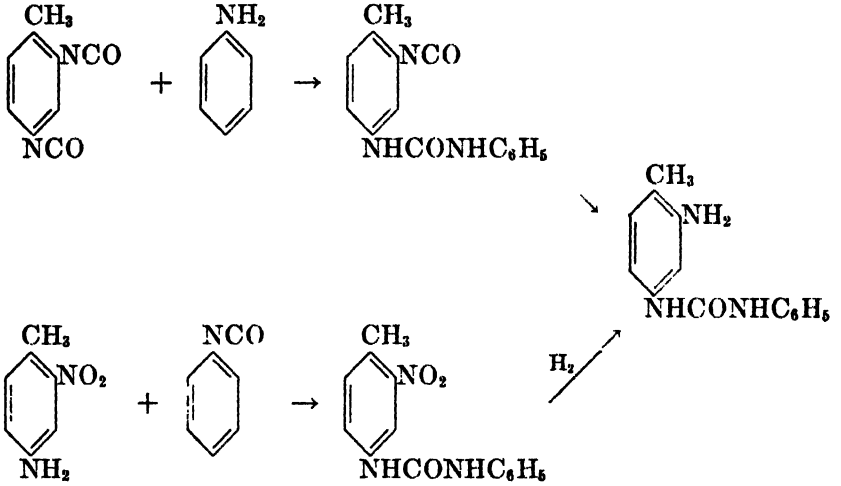
TABLE 10

Relative rate constants of RNCO *with methyl alcohol in di-n-butyl ether at 20°C.*

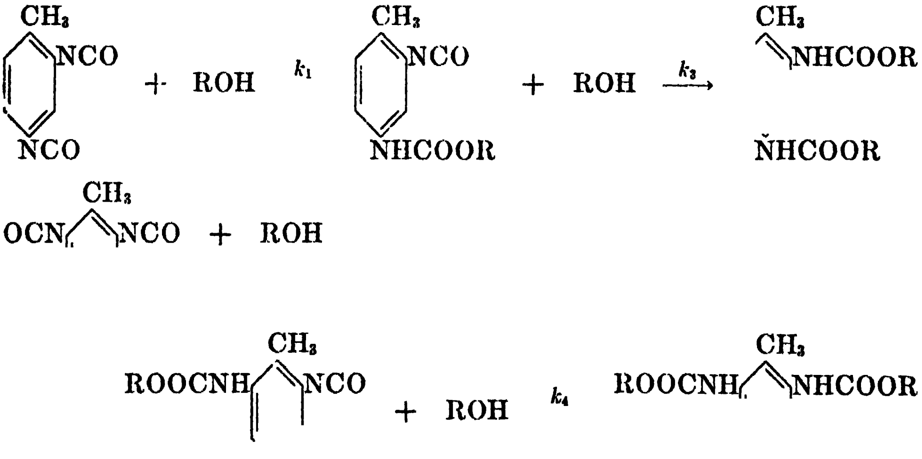
Catalyst, 0.0306 *M* triethylamine

			
471	586	1076	142,800

ing that this is also true for the para isocyanate group in toluene 2,4-diisocyanate. However, to prove the absence of any anomalous effects the difference in reactivity of the isocyanate groups was established by the following procedure (4): Toluene 2,4-diisocyanate (1 mole) was reacted with aniline (1 mole) in tetrahydrofuran solution and the residual isocyanate group hydrolyzed with hydrochloric acid. Fractional recrystallization of the product gave 68 per cent of the theoretical yield of a compound which proved to be identical with an authentic sample of 3-amino-4-methylcarbanilide, as judged by melting point, mixed melting point, and infrared spectra. The remaining 32 per cent of the material consisted predominantly of a mixture of the two isomeric carbanilides which could not be separated readily.

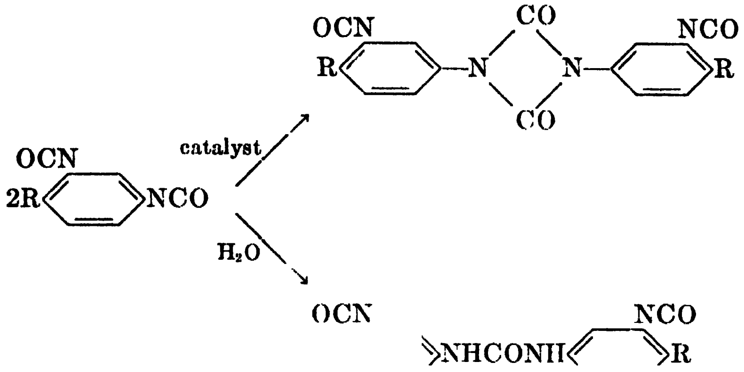


The preceding example indicates that the relative reactivities predicted from examination of the appropriate monoisocyanates are qualitatively correct in the case of toluene 2,4-diisocyanate. The following example, however, serves to demonstrate that predictions as to absolute reactivity are not justified.



As anticipated, k_1 is greater than k_2, but accurate measurements of k_3 and k_4 (210) show that the ratio $k_3/k_4 = \frac{1}{2}$. Thus, the reactivities of the two "ortho isocyanate" functions of the 2,4- and the 2,6-isomers differ by a factor of two, and neither is identical to that of the isocyanate function of *o*-tolyl isocyanate.

Among the diisocyanates of practical interest the most versatile are those bearing isocyanate groups which differ in their reactivity, since they allow the controlled stepwise synthesis of polymers or their intermediates. An example of the utilization of such differential reactivity is to be found in the preparation of diisocyanate dimers (17) and ureas (169), which are obtainable in high yield.



R = CH_3, CH_3O, or C_6H_5O.

In the preparation of polymers a degree of control over the orientation and structure of the segment derived from the diisocyanate is possible depending upon the magnitude of the difference in reactivity of the isocyanate groups.

VII. APPLICATION

An examination of the formal and the patent literature provides an indication of the scope and intensity of industrial research activity in the isocyanate field. A detailed discussion of the recent patent literature is not warranted. However, a generalized outline of the types of products in which isocyanates are finding application is presented.

The reaction of di- or polyfunctional isocyanates with reagents such as water, amines, alcohols, etc., is generally comparable to their monofunctional counterparts. No abnormal reactivity in polymeric systems has been reported, and in general the reaction rates observed have been independent of the polymeric species participating. Because of the great reactivity of isocyanates, however, their reactions are rarely if ever devoid of undesirable side reactions. For this reason reactions involving the synthesis of high-molecular-weight products are somewhat difficult to control and reproduce. In this latter respect, however, isocyanate reactions do not differ markedly from other condensation systems.

A. Fibers

Condensation polymerization resulting from the reaction of a compound containing at least two isocyanate groups with other polyfunctional reagents containing active hydrogen has opened a new and rapidly developing field in polymer chemistry. While many polymers have been investigated, only the linear polyurethans (Perlon U) derived from diols such as 1,4-butanediol and hexamethylene diisocyanate (18) are well known. They are usually made in aromatic chlorinated solvents at reflux.

$$O{=}C{=}N(CH_2)_6N{=}C{=}O \;+\; HO(CH_2)_4OH \rightleftharpoons$$

$$O{=}C{=}N(CH_2)_6NHCO{-}[O(CH_2)_4OCNH(CH_2)_6NHCO]_x{-}O(CH_2)_4OH \;+$$

$$52\ \text{cal./mole.}$$

$$\text{Molecular weight} \sim 10\text{–}12{,}000$$

These polymers are of interest as plastics and fibers because of their tensile strength, low water absorption, good electrical properties, and good resistance to outdoor exposure and acid. Their melting points are unusually sharp and attest to uniformity in molecular weight. The variation in melting point with structure is shown in table 11.

Polyurethans synthesized from hexamethylene diisocyanate and *cis*- and *trans*-2-butene-1,4-diol show small differences in properties, not attributable to cis-trans isomerism (144).

Polymers formed from 1,3-propanediol and 2,2-dimethyl-1,3-propanediol by reaction with hexamethylene diisocyanate are more crystalline than is that formed from 2-methyl-1,3-propanediol (31). Softening-point data are recorded in table 12.

B. Elastomers

The recent patent literature indicates an extensive interest in elastomers derived from isocyanates (6, 20, 21, 23, 32, 34, 35, 37, 58, 64, 70, 77, 99, 114–118,

TABLE 11

Melting points of some polyurethans

Number of Carbon Atoms in		Melting P	Number of Carbon Atoms in		Melting Point
Diisocyanate	Glycol		Diisocyanate	Glycol	
		°C.			°C.
4	4	190	6	5	159
4	6	180	6	9	147
4	10	170	12	12	128
6	3	167			

TABLE 12

Softening points of polyurethans formed from hexamethylene diisocyanate and glycols

Glycol	Softening Temperature of Polyurethan (Approximate)	Glycol	Softening Temperature of Polyurethan (Approximate)
	°C.		°C.
1,2-Ethanediol . . .	170	2-Methyl-1,3-propanediol .	50
1,3-Propanediol . . .	155	2,2-Dimethyl-1,3-propanediol	120
1,5-Pentanediol . . .	235		

120, 129, 131, 133, 143, 145–148, 155–159, 166, 168, 194, 197–201, 235–237, 239). The intermediates employed include polyether glycols, polyester glycols derived from aliphatic, aromatic, and unsaturated components, and polyester amides of molecular weights in general of 1000 or greater. Aromatic and aliphatic isocyanates and isothiocyanates and thermally unstable or reactive adducts of isocyanates have been used in the polymerizations. The products themselves range from liquids to solids, some of which must be immediately molded and cured and some of which are stable to storage. Curing of the raw polymers to form finished elastomeric articles is effected variously by simple heating of the initial reaction product or by heating in the presence of added polyisocyanate or active halogen compounds or, with polymers containing unsaturated linkages, free-radical promoters such as di-*tert*-butyl peroxide.

C. Plastics

Elastomers represent only one segment of the isocyanate polymer field. Relatively high-molecular-weight, linear, low-melting glycols and diamines, when polymerized with diisocyanates, are the basic intermediates for elastomeric products, whereas low-molecular-weight or highly crystalline, higher-molecular-weight difunctional alcohols, amines, carboxylic acids, etc., and polyfunctional reagents form, with di- and polyisocyanates, the basis for plastics, coatings, films, and fibers (22, 36, 39, 41, 49, 52, 53, 57, 62, 76, 98, 111–113, 119, 137–140, 158, 164, 165, 167, 173, 186, 187, 189, 191–193, 196, 216, 222, 223, 227, 234, 238). One product derived from aliphatic diamines and diisocyanates and bearing intralinear secondary amino functions which may be acylated or hydroxyalkylated is suggested as a plasma substitute (24). These products may be considered to be formed primarily by the reaction of isocyanates with alcohols, amines, carboxylic acids, water, and thiols, although often the intermediates are themselves preformed polyesters, polyamides, polyethers, polysiloxanes, and so on. There are also disclosed a few products which involve simultaneous reactions of not only isocyanate functions but other types of functional groups as well. In one example, a monoisocyanate bearing a carboxyl group is condensed with a diaminoalcohol to yield a fiber-forming polymer (224). In another, aromatic isocyanates bearing reactive halogen (benzyl) are polymerized in the presence of a Friedel–Crafts catalyst (74). A third example utilizes mono- or polyisocyanates which contain ethylenic bonds and which may be polymerized under such conditions that chain extension through reaction of both types of functions occurs (19).

D. Foams

Isocyanates, in their reactions with water and carboxylic acids, produce as a by-product of the polymerization a gas, carbon dioxide. As a consequence the polymerizing material is blown up to form a voluminous porous structure. When this phenomenon is properly controlled, foams with excellent structure and almost any desired density can be obtained (14, 15, 61, 63, 65, 67, 71, 75, 78–83, 90, 100, 106–108, 126, 209, 233). Depending upon the character of the intermediates these foams will be rigid or elastic. Foam "Prepolymers" are reaction products of di- or polyisocyanates with the same intermediates used in the formation of bulk elastomers and plastics with the difference that excess isocyanate is used so that a low-molecular-weight viscous fluid is formed. Addition of the final reactant such as water or dicarboxylic acid is made just prior to use, the mixture is poured into a mold, and chain extension, cross-linking, and foaming occur simultaneously.

E. Polymer modification

Mono-, di- and polyisocyanates have been used to cross-link or otherwise modify the properties of polymers which are not themselves formed from isocyanates. Such products include alkyd resins (208, 211), cellulose ethers or esters (181), polyamides (104, 185, 190), and polyurethans (188).

F. Adhesives and pigment-bonding systems

Isocyanates have been useful in the formulation of adhesives. Rubber may be bonded to polar substrates with the aid of isocyanates (95, 170). Condensation products of isocyanates with polymers bearing carboxyl groups (217) or other groups which will react with isocyanates (152) have been employed as adhesives.

G. Catalysts for isocyanate reactions

Although isocyanates are described as reactive compounds, aromatic much more so than aliphatic, it is often advantageous to accelerate reactions with catalysts. This is particularly true in the formation of foams. Isocyanate–water reactions are catalyzed by tertiary amines (234) and by inorganic acids such as sulfuric and phosphoric (134, 135). Reactions between isocyanates and alcohols or carboxylic acids are accelerated by tertiary amines or phosphines (132), beryllium hydroxide (48), colloidal or soluble iron compounds (131), lactams (174), and combinations of basic substances and neutral metallic compounds such as nickel carbonyl or iron acetonylacetonate (81).

H. Isocyanate generators

The extreme reactivity of isocyanates toward compounds containing active hydrogen makes them attractive as cross-linking or modifying agents for plastics, elastomers, resins, coating materials, textiles, and adhesives. In many of the above applications it is necessary to delay the desired isocyanate–substrate reaction until the final stages of fabrication or use. In order to achieve this objective certain isocyanate derivatives capable of undergoing thermal dissociation or exchange reactions with the active hydrogen site of the substrate are used to generate the isocyanate at the proper stage.

These isocyanate generators (16, 171) include the mono-, di-, or poly-reaction products of mono-, di-, or polyisocyanates with a secondary aromatic amine (16), tertiary alcohols (16, 105), amides (205, 238, 240), lactams (204, 238), monohydric phenols (203, 238), mercaptans (238), enolizable hydrogen compounds (16, 105, 171, 172, 203), heterocyclics (16, 69), hydrogen cyanide (171), and sodium bisulfite (16, 56, 171).

I. Miscellaneous

Other miscellaneous uses for isocyanates or polymers derived from them have been patented. These include the fixing of pigments on textiles and paper (46, 60, 66, 68), the bonding together or coating of fibers (51, 150, 182), and the preparation of cements of isocyanate-based polymers in appropriate solvents (30).

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RADICAL SUBSTITUTION IN AROMATIC NUCLEI

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I. INTRODUCTION

In the assignment of organic reaction mechanisms, radicals, defined as atoms or groups bearing unpaired electrons, have received far less study than ions as intermediates. The recurrent idea of polarity as a driving and orienting factor has overshadowed the line of thought traceable from Dumas, Gomberg, and Paneth. Doubtless one cause for this is simply that most preparative organic reactions are effected in solution, where ionization is favored.

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Nevertheless such radicals, well known to dominate the mechanism of gas-phase reaction, are now recognized as frequent participants in reactions in solution also. To be sure, the two environments are vastly different, but there is still profit in considering them together.

It is simpler to define radicals than to be sure that a reaction involves them. The transition from a radical mechanism to an ionic one is easy; it may occur upon change of substituents in a reactant, or addition of a polar catalyst, or use of a polar solvent (32). Moreover, it is likely that some reactions proceed by a mixture of radical and ionic mechanisms. In general, if a radical in solution is capable of being characterized by any physical means, it is too unreactive to cause direct aromatic substitution.

The presence of transient radicals is deduced from their effects. In aromatic substitution, this means (*a*) departure from the rules for activation and orientation in ionic attack and (*b*) more or less formation of biaryls. It is familiar that electron-attracting groups on a benzene ring produce deactivation of the ring toward cationic reagents and predominantly meta substitution thereby; electron-releasing groups have the same effects in anionic substitutions. If then an attacking reagent does not obey either of these rules, it must be neither cation nor anion, but a neutral atom or radical. Even in water, a solvent very favorable to ionization, radical mechanisms are quite possible (385) and indeed this solvent may be ideal for effecting radical reactions because of its great stability (100, 291).

Aromatic nuclei are defined (19, 135) so as to include the unsaturated heterocyclic compounds of special ring stability. Quinones are not considered aromatic compounds. Substitution, however, must be more arbitrarily delimited. In this paper, substitution is used to mean a *one-step reaction* (excluding intermediates that cannot be isolated) *in which a hydrogen atom on an aromatic nucleus* (ArH), *the substrate, becomes replaced by some atom or group other than another* H *or an* Ar *group derived directly from* ArH. There are few cases of replacement of an atom or group other than hydrogen in an electron-pairing reaction, so that their exclusion from this discussion is not a major one. To consider the production of symmetrical biaryls by oxidative or other elimination of hydrogen between two molecules of ArH would extend the review unduly.

Hey (200) has chosen to designate both

$$\mathrm{R\cdot + ArH \rightarrow ArR + H\cdot}$$

and

$$\mathrm{R\cdot + ArH \rightarrow RH + Ar\cdot}$$

as substitution processes, but it seems advisable to distinguish these as *ordinary* substitution and the first step of *transfer* substitution, respectively. This step has been called radicalotropy (129, 301). Transfer substitution in ArH is completed when the radical Ar•, recently called a "residual free radical of first order" (287), forms a bond with some atom other than hydrogen:

$$\mathrm{Ar\cdot + YZ \rightarrow ArY + Z\cdot}$$

or

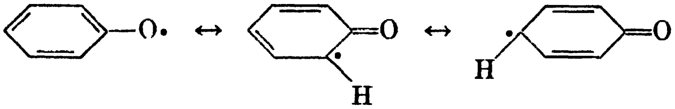
$$\mathrm{Ar\cdot + Y\cdot \rightarrow ArY}$$

Y• may even be R•; ordinary and transfer substitutions then yield exactly the same main products, but can sometimes be distinguished by the side effects of the differing intermediates H• and Ar•.

In recent years several reviews have touched upon homolytic aromatic substitution in solution (12, 121, 199, 200, 201, 234a, 306, 333, 392, 398), the more so since quantitative comparisons of the reactivity of intramolecular positions (orientation) and also corresponding positions on unlike molecules (partial rate factors) have become available. The present paper is intended to cover the subject up to January 1, 1955 and to include as many later pertinent references as possible. The nomenclature used follows that of *Chemical Abstracts*.

Foreword on orientation

Phenols and aromatic amines differ from other aromatic substrates for radical substitution in (*a*) their susceptibility to attack by radicals not otherwise active and (*b*) their great tendency with such radicals to yield no meta-substituted products. Both of these behaviors are due to the possibilities for resonance in the substituted aryl radical:



This stabilization of the radical favors its formation, in the same way that benzyl radicals are more easily formed and more stable than phenyl radicals. In any transfer substitution thus established, it is evident that when the radical reacts as if the unpaired electron were on the ring, and prototropy reëstablishes the aromatic structure, only ortho and/or para orientation can result.

II. ALKYLATION

Benzene is slowly methylated by lead tetraacetate in boiling acetic acid; the final product is benzyl acetate, because side-chain acetoxylation occurs subsequently. Chlorobenzene is likewise converted to isomeric chlorobenzyl acetates, of which only the para isomer has been characterized (136). Nitrobenzene gives chiefly *o*- and some *p*-nitrotoluene, each in small amount, and 1,8-dinitronaphthalene yields only a trace of 2-methyl-1,8-dinitronaphthalene. About 20 per cent of *m*-dinitrobenzene is converted to a mixture of its 4-methyl, 2,4-dimethyl, and 2,6-dimethyl derivatives; 1,3,5-trinitrobenzene goes to 2,4,6-trinitrotoluene and 2,4,6-trinitro-*m*-xylene; and 2,4,6-trinitrotoluene to the same xylene (136). 2,4,6-Trinitro-*m*-xylene itself resists further methylation (136, 345).

Alternatively such methylation of polynitro compounds can be effected with acetyl peroxide (136), anode-liberated radicals from the electrolysis of sodium acetate in acetic acid (136), or phenyl iodosoacetate (345). Tetraethyllead and tetramethyllead are ineffective agents (136) for the alkylation of benzene or naphthalene at temperatures up to 300°C. (93). Mercuric acetate is also ineffective (136); it seems probable that a more strongly oxidizing acetate such as nickelic or cobaltic acetate would be better. If the aromatic substrate is not nitrated and carries an alkyl side chain, this rather than the ring is attacked (259, 328).

The alkylation of pyridine occurs in the 2-position (predominantly) and 4-position or both, presumably by transfer substitution. The yields obtained by using diacyl peroxides are very satisfactory, whereas those from the electrolysis of a fatty acid in pyridine are only 4–14 per cent (168) (see table 1). In another example of alkylation in a heterocyclic nucleus, methyl 2-phenyloxazole-4-carboxylate with lead tetraacetate gains a methyl group in the 5-position (89).

Carboxymethylation of aromatic substrates has been observed, obviously as a transfer substitution. In the treatment of the three cresols and 2,4-xylenol with acetyl peroxide in acetic acid, a $—CH_2COOH$ group may enter any one of the unoccupied sites ortho or para to the hydroxyl group (398). The radical evidently arises from the solvent

$$CH_3COO\cdot \text{ (or } CH_3\cdot) + CH_3COOH \rightarrow \cdot CH_2COOH + CH_3COOH \text{ (or } CH_4)$$

and combines with a mesomeric radical derived from the phenol (compare page 79). In the same way the decomposition of benzoyl peroxide in acetic acid gives rise to appreciable amounts of α-carboxy-*o*-toluic acid and α-carboxy-*p*-toluic acid (164).

Other examples of the ability of benzoyl peroxide to yield such alkylated benzoic acids are available. Its decomposition in chloroform or carbon tetrachloride gives *o*- and *p*-trichloromethylbenzoic acids (48, 155, 234, 251), in *n*-octane it produces what is probably *p*-*n*-octylbenzoic acid (47), and in cyclohexane it forms *o*- and *p*-cyclohexylbenzoic acids as well as more complex ones (192).

The 2-cyano-2-propyl radical from 2,2′-azobis(2-methylpropionitrile) does not alkylate *m*-dinitrobenzene or 1,3,5-trinitrobenzene in boiling toluene (163).

Nuclear benzylation of toluene or *o*-chlorotoluene is not brought about by phenylacetyl peroxide (33), but *N*-benzyl-*N*-nitrosoacetamide does produce small yields of diarylmethanes from benzene, toluene, and chlorobenzene, by way of either benzyl or benzylidene radicals (174).

The rearrangement of benzyl phenyl ethers in quinoline produces not only

TABLE 1

Radical alkylations of pyridine (168)

Source of radical (R) introduced	Ratio of 2 isomer to 4 isomer	Overall Yield
		per cent
Electrolysis of RCOOH: R =		
CH_3	2.8:1	3.5
C_2H_5	1.3-2.8:1[*]	14
n-C_3H_7	5.1:1	4
Pyrolysis of $(RCOO)_2$· R =		
CH_3	7.6:1	86
C_2H_5	2.1:1[*]	87
n-C_3H_7	2.4:1	84
n-$C_{11}H_{23}$	3:1	38

[*] A small amount of 2,4-diethylpyridine was formed.

the expected benzylphenols, but benzylquinolines and hydroxyphenylquinolines also, by participation of the solvent (212, 213). Benzyl radicals from the pyrolysis of benzyl *p*-toluenesulfonate benzylate chlorobenzene in the para position but do not affect nitrobenzene so (310).

Alkylation, like phenylation, can be caused by heating an aromatic substrate with a suitable Grignard reagent (258) or its aluminum counterpart (388, 389), para orientation being observed in the few cases studied. No doubt some homolytic cleavage of such organometallic reagents does occur, especially when there is an acceptor for the radical (260). Yet it remains very uncertain whether to classify such alkylations and arylations as radical or as carbanion substitutions (149).

A remarkable alkylation of pyridine is its conversion to 4-(α-benzoyloxybenzyl)pyridine, 4-$C_6H_5CH(OCOC_6H_5)C_5H_4N$, by heating with benzaldehyde and *tert*-butyl peroxide. The steps are tentatively formulated as (*a*) generation of *tert*-butoxy radicals, (*b*) conversion thereby of benzaldehyde to benzoyl radicals, (*c*) reaction of benzoyl radicals with benzaldehyde to yield α-benzoyloxybenzyl radicals, $C_6H_5(C_6H_5COO)CH\cdot$, (*d*) 1,4-addition of either benzoyl and α-benzoyloxybenzyl or of two α-benzoyloxybenzyl radicals to pyridine, and (*e*) pyrolytic reversion to a pyridine structure (263).

The suggestion that thermal rearrangements of aryl allyl ethers, at least those yielding *p*-allylphenols, involve the migration of radicals (303) has not been accepted (69, 383). However, the arguments against a radical mechanism (232) do not necessarily apply when the reaction is caused photochemically; even diphenyl ether so rearranges to *p*-phenylphenol (264). Another classical reaction, the Elbs cyclization, may involve radicals also (20).

Triarylmethyl radicals are so stabilized that they rarely substitute directly in aromatic substrates such as benzene, although they attack the methyl group in toluene (124) and the nitro group in nitrobenzene (178). The radicals themselves interact by thermal disproportionation (411),

$$2(C_6H_5)_3C\cdot \rightarrow p\text{-}(C_6H_5)_2CHC_6H_4C(C_6H_5)_3$$

or further combine with diphenylnitrogen oxide, itself a radical (414),

$$2(C_6H_5)_3C\cdot + (C_6H_5)_2NO \rightarrow p\text{-}(C_6H_5)_3CC_6H_4C(C_6H_5)_2ON(C_6H_5)_2$$

but the mechanism of these nuclear substitutions is obscure.

The only other record of direct triphenylmethylation is that of boiling *o*-xylene and *p*-xylene. Orientation was not reported, and the anomalous failure of *m*-xylene to react similarly (411) suggests the need of further study.

Nuclear triphenylmethylation of phenol by the radical (350) surely proceeds by transfer substitution. It is doubtful whether similar substitution of phenols, phenolic ethers, amines, and acetylated amines by heating with chlorotriphenylmethane is to be assigned a radical (282) or a carbonium-ion course.

Benzene, toluene, chlorobenzene, and methyl benzoate can undergo substitution if they are first converted to aryl radicals. The necessary activating radical can come from an aroyl peroxide.

$$(ArCOO)_2 + (C_6H_5)_3C\cdot \rightarrow ArCOOC(C_6H_5)_3 + ArCOO\cdot$$

$$ArCOO\cdot + Ar'H \rightarrow ArCOOH + Ar'\cdot$$

$$Ar'\cdot + (C_6H_5)_3C\cdot \rightarrow (C_6H_5)_3CAr'$$

Little formation of carbon dioxide and none of any biaryl or $(C_6H_5)_3CAr$ was observed. Exclusively para substitution was noted (410, 412).

Only two isolated examples of nuclear acylation have been interpreted as involving radicals. The thermal reaction of either benzoyltriphenylmethyldiimide (409), $C_6H_5CON{=}NC(C_6H_5)_3$, or β-benzopinacolone (412), $C_6H_5COC(C_6H_5)_3$, yields 4-triphenylmethylbenzophenone in a rearrangement probably analogous to the noncyclizing disproportionation of triphenylmethyl itself. It is ventured here that the Fries-like rearrangement of phenolic esters such as phenyl cyclohexanecarboxylate and phenyl 3-methyl-2-butanoate into *o*-hydroxy ketones,

$$RCOOC_6H_5 \rightarrow o\text{-}HOC_6H_4COR$$

which is thermal instead of catalytic (230), proceeds by way of acyl radicals.

Under favorable circumstances an alkylidene biradical, RCH: or R_2C:, can substitute in an aromatic ring. Thus when α-toluenesulfonyl azide is thermally decomposed in aniline or dimethylaniline, some sulfur dioxide and nitrogen are evolved and 4,4′-diaminotriphenylmethane or 4,4′-bis(dimethylamino)triphenylmethane is formed (97). The diphenylmethylene radical, $(C_6H_5)_2C$:, from diazodiphenylmethane, does not attack benzene (354) and takes hydrogen from the side chain of benzyl methyl ether (28), but with phenol it gives small amounts (2 to 3 per cent) of *o*-(diphenylmethyl)phenol (61, 356). The ethoxycarbonylmethylene radical, C_2H_5OCOCH:, derived from ethyl diazoacetate, is well known to add to a benzene ring and yield a bicyclo compound containing a cyclopropane ring. This upon heating isomerizes to cycloheptane derivatives related to the tropolones (247). However, alkyl aryl ethers heated with ethyl diazoacetate yield no cyclopropane derivatives but give, among other products, small amounts of ethyl alkoxyarylacetates.

$$C_6H_5OR + N_2CHCOOC_2H_5 \rightarrow ROC_6H_4CH_2COOC_2H_5$$

Anisole was thus converted to the 4-substituted compound, 1,2-dimethoxybenzene to the 4-substituted compound, and 1-methoxynaphthalene to a similar but unidentified product, *not* ethyl 1-(4-methoxynaphthalene)acetate. 2-Methoxynaphthalene gave a 33 per cent yield of the 1-methoxycarbonylated product, and even mesitylene undergoes the substitution. A carbonium-ion sequence has been suggested for this unusual process (170), but a radical attack, comparable to sulfonamidation (see page 99), seems equally likely at present.

III. INTERMOLECULAR ARYLATION

There are several reasons why arylation is the best-studied radical substitution. The radical source—most commonly some form of a diazo compound or an aroyl peroxide—is readily obtainable, the products are usually crystalline and reasonably identifiable, and there is no abundance of syntheses for biaryls. Radicals are almost surely involved also in the Ullmann reaction and the production of biaryls by dehydrogenation, but these will not be considered here.

A. Arylation with diazotates and diazoacetates

Reactions of this category have been reviewed in detail (16). Table 2 supplements the earlier data primarily by description of work published since 1944. No doubt some of the reactions tabulated are partially ionic in character, e.g., those of diazonium trifluoroacetates, which are discussed below. In some instances wherein metal powders or metallic salts were added, proof of a homolytic course of reaction is lacking.

In table 4 ratios of isomeric arylation products from these reactions and from the pyrolysis of peroxides have been tabulated. It should be noted that these ratios do not show a preponderance of the para compounds, as formerly believed. In this respect recent work is more reliable because new analytical tools and techniques have become available. Indeed, the ratios of isomers obtained from preparative experiments are not safe to use in the derivation of partial rate factors (211).

A recent study (315) has been made of the formation of biphenyls from arylamines nitrosated with alkyl nitrite–trifluoroacetic anhydride mixtures, from aqueous diazonium trifluoroacetates, from diazonium chlorides with added trifluoroacetate ions, and from diazonium salts stabilized as the water-insoluble acid trifluoroacetates (see table 2). An equilibrium probably exists between an ionic and some covalent type of structure, the latter producing homolytic substitutions. There must be, however, only a little of the covalent material, since diazonium acid trifluoroacetates appear to be largely dissociated in dilute aqueous solutions.

Whatever the mechanisms of copper-catalyzed reactions of diazo compounds, little doubt exists that homolytic substitution is sometimes involved. Thus, when benzenediazonium formate is decomposed in acetic acid containing copper powder (161), *p*-terphenyl is produced. The addition of copper powder and glacial formic acid to aniline diazotized in glacial acetic acid results in the formation of *p*-terphenyl, *p*-quaterphenyl, and *p*-quinquephenyl. Benzenediazonium sulfate in the presence of alcohol and copper powder (162) gives the same products. Biphenyl, *p*-terphenyl, and *p*-quaterphenyl are produced when *p*-biphenyldiazonium sulfate is decomposed in a mixture of benzene, glacial formic acid, and copper powder.

The exceptional reactivity of ferrocene as a substrate for arylation (312a) deserves notice.

B. Arylation with triazenes (diazoamino compounds)

The pyrolysis of 1,3-diphenyltriazene yields a mixture of 2- and 4-biphenylamines; the orientation is characteristic of homolytic as well as electrophilic substitution (197, 215). 1,3-Di-*p*-tolyltriazene behaves similarly, yielding about

TABLE 2

Arylated products from diazo compounds[a]

Product	Component A	Component B	Method[b]	Yield	Reference
		Monosubstituted biphenyls, $RC_6H_4C_6H_5$			
				per cent	
R =					
H	$C_6H_5NH_2$	C_6H_6	A-1	19	(174)
				15	(359)
			A-2	19	(174)
				22	(130)
			A-3	16	(130)
			A-6	5-30	(315)
			A-7	7-19	(315)
			A-9	33	(299)
			B-1	40-80	(174)
			B	5	(227)
			B-3	32-49	(315)
2-, 3-, and 4-CH_3	$C_6H_5NH_2$	$C_6H_5CH_3$	B-2	9, 27	(342)
4-CH_3	p-$CH_3C_6H_4NH_2$	C_6H_6	A-1	14	(64)
			A-4	43	(315)
			A-7	8	(315)
	$C_6H_5NH_2$	$C_6H_5CH_3$	A-9	—	(298)
	p-$CH_3C_6H_4NH_2$	C_6H_6	B-3	16-37	(315)
(?)-CH_3	$C_6H_5NH_2$	$C_6H_5CH_3$	B-1	49	(174)
2-, 3-, and 4-$(CH_3)_2CH$	$C_6H_5NH_2$	$C_6H_5CH(CH_3)_2$	B-2	22, 24	(342)
2-, 3-, and 4-$(CH_3)_3C$	$C_6H_5NH_2$	$C_6H_5C(CH_3)_3$	B-2	22, 25	(342)
4-$(CH_3)_3C$	p-$(CH_3)_3CC_6H_4NH_2$	C_6H_6	B-1	—	(66)
2-HO	$C_6H_5NH_2$	C_6H_5OH	A-6	2	(309)
2- and 4-HO	$C_6H_5NH_2$	C_6H_5OH	A-6	>27	(214)
4-HO	$C_6H_5NH_2$	C_6H_5OH	A-4[c]	26	(216)
			A-6	27	(309)
(?)-C_2H_5OOC	$C_6H_5NH_2$	$C_6H_5COOC_2H_5$	B-1	—	(174)
2-C_6H_5CO	2-$H_2NC_6H_4COC_6H_5$	C_6H_6	A-1	15	(117)
			B-2	15	(118)
2-CH_3O	$C_6H_5NH_2$	$C_6H_5OCH_3$	A-2	15	(126)
4-CH_3O	p-$CH_3OC_6H_4NH_2$	C_6H_6	A-6	25	(315)
			B-3	12	(315)
2-C_6H_5O	o-$C_6H_5OC_6H_4NH_2$	C_6H_6	A-1	25	(117)
2- and 4-O_2N	$C_6H_5NH_2$	$C_6H_5NO_2$	A-1	6	(174)
			A-2	8	(174)
2-, 3-, and 4-O_2N	$C_6H_5NH_2$	$C_6H_5NO_2$	A-1	—	(11)
				13-15	(359)
			B-2	39-53	(119)
			B	30-37	(359)
3-O_2N	m-$O_2NC_6H_4NH_2$	C_6H_6	A-1	21	(243)
			A-2	18	(130)
			A-3	—	(116)
			B-1	63	(146)
4-O_2N	p $O_2NC_6H_4NH_2$	C_6H_6	A-2	26	(130)
			A-6	11	(315)
			B-3	6, 14	(315)
			B[d]	—	(270)
3-F_3C	m-$CF_3C_6H_4NH_2$	C_6H_6	B-1	35	(314)
4-F_3C	p-$CF_3C_6H_4NH_2$	C_6H_6	A-6	17	(315)
			B-3	23	(315)
2-Cl	o-$ClC_6H_4NH_2$	C_6H_6	A-1	13	(14)
(?)-Cl	$C_6H_5NH_2$	C_6H_5Cl	A-1	16, 33	(14)
3-Cl	m-$ClC_6H_4NH_2$	C_6H_6	A-1	22	(14)
4-Cl	p-$ClC_6H_4NH_2$	C_6H_6	A-1	28	(14)
			A-4	18-25	(315)
			A-6	12	(315)
			A-7	9	(315)
			B-3	17, 33	(315)

TABLE 2—*Continued*

Product	Component A	Component B	Method$^{(b)}$	Yield	Reference
Disubstituted biphenyls, RR'$C_6H_3C_6H_5$					
				per cent	
R and R' =					
2-CH_3-4-HO	$C_6H_5NH_2$	*m*-$CH_3C_6H_4OH$	A-6	10-15	(74)
3-CH_3-4-HO	$C_6H_5NH_2$	*o*-$CH_3C_6H_4OH$	A-6	10-15	(74)
3-CH_3-4-O_2N	3-CH_3-4-$O_2NC_6H_3NH_2$	C_6H_6	A-2	—	(174)
4-CH_3-2-O_2N	4-CH_3-2-$O_2NC_6H_3NH_2$	C_6H_6	A-3	40	(337)
				—	(68)
3,4-$(HO)_2$	$C_6H_5NH_2$	*o*-$C_6H_4(OH)_2$	A-6	11	(309)
3-O_2N-2-CH_3OOC	2-H_2N-6-$O_2NC_6H_3COOCH_3$	C_6H_6	A-1	7	(228)
3,4-$(C_2H_5OOC)_2$	4-H_2N-1,2-$C_6H_3(COOC_2H_5)_2$	C_6H_6	B-2	45	(184)
3,4-$(CN)_2$	4-H_2N-1,2-$C_6H_3(CN)_2$	C_6H_6	A-1	57	(184)
4-O_2N-3-CF_3	4-O_2N-3-$CF_3C_6H_3NH_2$	C_6H_6	A-3	22	(314)
Disubstituted biphenyls, $RC_6H_4C_6H_4R'$					
R and R' =					
4,4'-$(CH_3)_2$	*p*-$CH_3C_6H_4NH_2$	$C_6H_5CH_3$	A-4	2	(315)
4'-CH_3-4-CH_3OOC	*p*-$CH_3C_6H_4NH_2$	$C_6H_5COOCH_3$	A-4	1	(315)
4-CH_3-2'- and 4'-O_2N	*p*-$CH_3C_6H_4NH_2$	$C_6H_5NO_2$	A-2	—	(204)
4-CH_3-2'-, 3'-, and 4'-O_2N	*p*-$CH_3C_6H_4NH_2$	$C_6H_5NO_2$	A-1	27-45	(204)
			B-2	28-32	(204)
2- and 4-CH_3-3'-O_2N	*m*-$O_2NC_6H_4NH_2$	$C_6H_5CH_3$	A-3	19	(204)
2- and 4-CH_3-4'-O_2N	*p*-$O_2NC_6H_4NH_2$	$C_6H_5CH_3$	B$^{(d)}$	—	(270, 272)
4,4'-$(HO)_2$	*p*-$HOC_6H_4NH_2$	C_6H_5OH	A-4$^{(c)}$	41	(216)
4'-CH_3O-4-HO	*p*-$CH_3OC_6H_4NH_2$	C_6H_5OH	A-4$^{(c)}$	36	(216)
2'- and 4'-HO-2-HOOC	*o*-$H_2NC_6H_4COOH$	C_6H_5OH	A-6$^{(e)}$	—	(171, 173)
4'-Cl-4-HO	*p*-$ClC_6H_4NH_2$	C_6H_5OH	A-4$^{(c)}$	31	(216)
4'-O_2N-4-HOOC	*p*-$O_2NC_6H_4NH_2$	C_6H_5COOH	B	—	(271)
4'-O_2N-4-$HOCH_2$	*p*-$O_2NC_6H_4NH_2$	$C_6H_5CH_2OH$	B	—	(271)
4'-O_2N-4-HCO	*p*-$O_2NC_6H_4NH_2$	C_6H_5CHO	B	—	(271)
4'-O_2N-4-CH_3CO	*p*-$O_2NC_6H_4NH_2$	$C_6H_5COCH_3$	B	—	(271)
2,4'- and 4,4'-$(O_2N)_2$	*p*-$O_2NC_6H_4NH_2$	$C_6H_5NO_2$	B	—	(272)
3,4'-$(O_2N)_2$	*m*-$O_2NC_6H_4NH_2$	$C_6H_5NO_2$	B-2	12	(70)
2-CH_3O-3'-O_2N	*m*-$O_2NC_6H_4NH_2$	$C_6H_5OCH_3$	A-2	50	(126)
			B-1	47	(126)
4-C_2H_5O-4'-O_2N	*p*-$O_2NC_6H_4NH_2$	$C_6H_5OC_2H_5$	B$^{(f)}$	—	(271)
4-Br-2'-, 3'-, and 4'-O_2N	*p*-$BrC_6H_4NH_2$	$C_6H_5NO_2$	A-1	16-25	(204)
			B-2	34-44	(204)
2,4'-$(CH_3O)_2$	*p*-$CH_3OC_6H_4NH_2$	$C_6H_5OCH_3$	B-1	—	(126)
Fluorenone	2-$C_6H_5COC_6H_4NH_2$		A-1	1	(117)
3-Chlorofluorenone	2-(4-$ClC_6H_4CO)C_6H_4NH_2$		A-6	—	(44)
Polysubstituted biphenyls					
5,2'-$(CH_3)_2$ 2-HO	*o*-$CH_3C_6H_4NH_2$	*p*-$CH_3C_6H_4OH$	A-6	10-15	(74)
5,3'-$(CH_3)_2$-2-HO	*m*-$CH_3C_6H_4NH_2$	*p*-$CH_3C_6H_4OH$	A-6	10-15	(74)
5,4'-$(CH_3)_2$-2-HO	*p*-$CH_3C_6H_4NH_2$	*p*-$CH_3C_6H_4OH$	A-6	10-15	(74)
2,2'-$(CH_3)_2$-4-HO	*o*-$CH_3C_6H_4NH_2$	*m*-$CH_3C_6H_4OH$	A-6	10-15	(74)
2,3'-$(CH_3)_2$-4-HO	*m* $CH_3C_6H_4NH_2$	*m*-$CH_3C_6H_4OH$	A-6	10-15	(74)
2,4'-$(CH_3)_2$-4-HO	*p*-$CH_3C_6H_4NH_2$	*m*-$CH_3C_6H_4OH$	A-6	10-15	(74)
3,2'-$(CH_3)_2$-4-HO	*o*-$CH_3C_6H_4NH_2$	*o*-$CH_3C_6H_4OH$	A-6	10-15	(74)
3,3'-$(CH_3)_2$-4-HO	*m*-$CH_3C_6H_4NH_2$	*o*-$CH_3C_6H_4OH$	A-6	10-15	(74)
3,4'-$(CH_3)_2$-4-HO	*p*-$CH_3C_6H_4NH_2$	*o*-$CH_3C_6H_4OH$	A-6	10-15	(74)
2'-HO-3-Cl-2-HOOC	2-H_2N-6-ClC_6H_3COOH	C_6H_5OH	A-6	3	(229)
2'-HO-4-Cl-2-HOOC	2-H_2N-4-ClC_6H_3COOH	C_6H_5OH	A-6	10	(229)
3,4,5-$(CH_3OOC)_3$	5-H_2N-1,2,3-$C_6H_2(COOCH_3)_3$	C_6H_6	B-2	60	(317)
2'-, 3'-, and 4'-CH_3O-3,4-$(CN)_2$	4-H_2N-1,2-$C_6H_3(CN)_2$	$C_6H_5OCH_3$	A-1	—	(184)

TABLE 2—*Continued*

Product	Component A	Component B	Method[(b)]	Yield	Reference
Terphenyls and derivatives					
				per cent	
o-Terphenyl, 2-CH_3-6-O_2N	*o*-(2-CH_3-6-$O_2NC_6H_3$)$C_6H_4NH_2$	C_6H_6	A-1	13–16	(115)
m-Terphenyl	*m*-$C_6H_5C_6H_4NH_2$	C_6H_6	B-2	35	(70)
4,4′,4″-$(O_2N)_3$ and others	5-O_2N-1,3-$C_6H_3(NH_2)_2$	$C_6H_5NO_2$	B-2	19	(70)
p-Terphenyl[(g)]	$C_6H_5NH_2$	$C_6H_5C_6H_5$	A-9	—	(298)
4,4″-$(O_2N)_2$-3-(4-$O_2NC_6H_4$)-2′,5′-$(H_2N)_2$	*p*-$O_2NC_6H_4NH_2$	*p*-$C_6H_4(NH_2)_2$	A-6	27	(6)
2,2″-$(O_2N)_2$-3′,6′-(2-$O_2NC_6H_4$)-2′,5′-$(H_2N)_2$	*o*-$O_2NC_6H_4NH_2$	*p*-$C_6H_4(NH_2)_2$	A-6	81	(6)
2,5,2″,5″-Cl_4-3′-(2,5-$Cl_2C_6H_3$)-2′,5′-$(H_2N)_2$	2,5-$Cl_2C_6H_3NH_2$	*p*-$C_6H_4(NH_2)_2$	A-6	23	(6)
Quaterphenyls, 4-CH_3	*p*-$CH_3C_6H_4NH_2$	C_6H_6	A-1	—	(64)
Arylnaphthalenes					
1- and 2-C_6H_5	$C_6H_5NH_2$	$C_{10}H_8$	A-9 B	— 38[(h)]	(297) (227)
1-(4-HOC_6H_4)	1-$C_{10}H_7NH_2$	C_6H_5OH	A-4	29	(216)
2-(4-HOC_6H_4)	2-$C_{10}H_7NH_2$	C_6H_5OH	A-4	35	(216)
2-(2- and 4-$O_2NC_6H_4$)	2-$C_{10}H_7NH_2$	$C_6H_5NO_2$	B-1, B-2	--	(202)
(?)-(4-$O_2NC_6H_4$)	*p*-$O_2NC_6H_4NH_2$	$C_{10}H_8$	B	—	(272)
2-CH_3-(?)-C_6H_5[(i)]	$C_6H_5NH_2$	2-$CH_3C_{10}H_7$	B	—	(227)
2,7-$(C_6H_5)_2$	2,7-$C_{10}H_6(NH_2)_2$	C_6H_6	B-1	—	(202)
6-CH_3O-2-C_6H_5	6-CH_3O-2-$C_{10}H_6NH_2$	C_6H_6	B-1	41	(202)
7-CH_3O-2-C_6H_5	7-CH_3O 2-$C_{10}H_6NH_2$	C_6H_6	B-1	44	(202)
1-O_2N-2-C_6H_5	1-O_2N-2-$C_{10}H_6NH_2$	C_6H_6	A-1	—	(202)
5-O_2N-2-C_6H_5	5-O_2N-2-$C_{10}H_6NH_2$	C_6H_6	B-1	40	(202)
6-O_2N-2-C_6H_5	6-O_2N-2-$C_{10}H_6NH_2$	C_6H_6	B-1	52	(202)
8-O_2N-2-C_6H_5	8-O_2N-2-$C_{10}H_6NH_2$	C_6H_6	B-1	47	(202)
6-Br-2-C_6H_5	6-Br-2-$C_{10}H_6NH_2$	C_6H_6	B-1	44	(202)
2,6-$(CH_3)_2$-1-C_6H_5	$C_6H_5NH_2$	2,6-$(CH_3)_2C_{10}H_6$	B	49.5[(j)]	(227)
Arylfurans					
2-C_6H_5	$C_6H_5NH_2$	Furan	A-1	22	(246)
2-(4-$O_2NC_6H_4$)	*p*-$O_2NC_6H_4$	Furan	A-3	20	(246)
2-(4-ClC_6H_4)	*p*-$ClC_6H_4NH_2$	Furan	B-2	19	(246)
2- and 3-(4-ClC_6H_4)	*p*-$ClC_6H_4NH_2$	Furan	A-1	29	(246)
2-(4-BrC_6H_4)	*p*-$BrC_6H_4NH_2$	Furan	A-1	15	(246)
2-(1-$C_{10}H_7$)	1-$C_{10}H_7NH_2$	Furan	A-3	18	(246)
Arylthiophenes					
3-C_6H_5	$C_6H_5NH_2$	C_4H_4S	A-9	—	(298)
2-(4-$CH_3C_6H_4$)	*p*-$CH_3C_6H_4NH_2$	C_4H_4S	A-1	13	(63)
2-(2-$O_2NC_6H_4$)	*o*-$O_2NC_6H_4NH_2$	C_4H_4S	A-3	51	(364)
2-(4-ClC_6H_4)	*p*-$ClC_6H_4NH_2$	C_4H_4S	A-1	33	(63)
2,5-(4-$CH_3C_6H_4)_2$	*p*-$CH_3C_6H_4NH_2$	C_4H_4S	A-1	3	(63)
2,5-(4-$ClC_6H_4)_2$	*p*-$ClC_6H_4NH_2$	C_4H_4S	A-1	2	(63)
2-C_6H_5-thianaphthene	$C_6H_5NH_2$	Thianaphthene	B-1	5	(150)
Dibenzothiophene	2-$C_6H_5SC_6H_4NH_2$		A-1	10	(117)

TABLE 2—*Continued*

Product	Component A	Component B	Method[(b)]	Yield	Reference
Arylated heterocyclic nitrogen compounds					
				per cent	
Pyridines:					
2- and 4-C_6H_5	$C_6H_5NH_2$	C_5H_5N	A-5	21	(298)
3-C_6H_5	3-$H_2NC_5H_4N$	C_6H_6	B-2[(k)]	39	(323)
2-(2- and 4-HOC_6H_4)	2-$H_2NC_5H_4N$	C_6H_5OH	A-2	—	(75, 76)
2-(4-$O_2NC_6H_4$)	*p*-$O_2NC_6H_4NH_2$	C_5H_5N	B	—	(272)
4-(4-$O_2NC_6H_4$)	*p*-$O_2NC_6H_4NH_2$	C_5H_5N	A-5	28	(391)
2-(4-BrC_6H_4) and isomers	*p*-$BrC_6H_4NH_2$	C_5H_5N	B-2	7	(208a)
2-, 3-, and 4-(4-$(CH_3)_3C$-2-$O_2NC_6H_3$)	4-$(CH_3)_3C$-2-$O_2NC_6H_3NH_2$	C_5H_5N	A 5	30	(82)
2-, 3-, and 4-(4-$(CH_3)_3C$-3-$O_2NC_6H_3$)	4-$(CH_3)_3C$-3-$O_2NC_6H_3NH_2$	C_5H_5N	A-5	59	(82)
2-, 3-, and 4-(3,4-$(C_2H_5OOC)_2C_6H_3$)	4-H_2N-1,2-$C_6H_3(COOC_2H_5)_2$	C_5H_5N	A-5	40	(184)
2-, 3-, and 4-(3,4-$(CN)_2C_6H_3$)	4-H_2N-1,2-$C_6H_3(CN)_2$	C_5H_5N	A-5	—	(184)
2-, 3-, and 4-(5-CH_3O-2-$O_2NC_6H_3$)	5-CH_3O-2-$O_2NC_6H_3NH_2$	C_5H_5N	A-5	22	(82)
4-(4-$(CH_3)_2NC_6H_4$)	*p*-$(CH_3)_2NC_6H_4NH_2$	C_5H_5N	A-5	—	(266)
2-(4-$C_6H_5NHC_6H_4$)	*p*-$C_6H_5NHC_6H_4NH_2$	C_5H_5N	A-5	—	(86)
(*m*-C_6H_4=)di-	(?)-(*m*-$H_2NC_6H_4$)C_5H_4N	C_5H_5N	A-5	—	(85)
(*p*-C_6H_4=)di-	(?)-(*p*-$H_2NC_6H_4$)C_5H_4N	C_5H_5N	A-5	—	(85)
2-, 3-, and 4-(3-*o*-$\underline{CONHCOC}_6H_4$)	3-Aminophthalimide	C_5H_5N	A-5	85	(184)
2-, 3-, and 4-(4-*o*-$\underline{CONHCOC}_6H_4$)	4-Aminophthalimide	C_5H_5N	A-5	56	(184)
2-, 3-, and 4-(2-phthalimido-5-methoxyphenyl)	*N*-(2-Amino-4-methoxyphenyl)phthalimide	C_5H_5N	A-5	—	(82)
2-, 3-, and 4-(3,4-$Cl_2C_6H_3$)	3,4-$Cl_2C_6H_3NH_2$	C_5H_5N	A-5	—	(184)
2-,3-, and 4-(3,4-$Br_2C_6H_3$)	3,4-$Br_2C_6H_3NH_2$	C_5H_5N	A 5	—	(184)
2-*n*-C_4H_9O-5-C_6H_5	5-H_2N-2-*n*-$C_4H_9OC_5H_3N$	C_6H_6	A-1	14	(3)
2-Cl-3-C_6H_5	3-H_2N-2-ClC_5H_3N	C_6H_6	B-2	—	(3)
2-Cl-5-C_6H_5	5-H_2N-2-ClC_5H_3N	C_6H_6	A-3	—	(3)
			B-2	22	(3)
Quinolines:					
3-C_6H_5	3-$H_2NC_9H_6N$	C_6H_6	B-2	33	(3)
(?)-(3-$O_2NC_6H_4$)	*p*-$O_2NC_6H_4NH_2$	C_9H_7N	B	—	(272)
3-(2- and 3-C_5H_4N)	3-$H_2NC_9H_6N$	C_5H_5N	A-5	48	(51)
3-(2- and 4-C_5H_4N)	3-$H_2NC_9H_6N$	C_5H_5N	A-5	39	(1)
5-(2- and other C_5H_4N)	5-$H_2NC_9H_6N$	C_5H_5N	A-5	29	(81, 83)
8-(2-, 3-, and 4-C_5H_4N)	8-$H_2NC_9H_6N$	C_5H_5N	A-5	15	(81, 83)
4-CH_3-3-(?-C_5H_4N)	3-H_2N-4-$CH_3C_9H_5N$	C_5H_5N	A-5	—	(355)
6-CH_3O-8-(2-, 3-, and 4-C_5H_4N)	8-H_2N-6-$CH_3OC_9H_5N$	C_5H_5N	A-5	—	(82, 83)
8-CH_3O-6-(2-, 3-, and 4-C_5H_4N)	6-H_2N-8-$CH_3OC_9H_5N$	C_5H_5N	A-5	—	(83)
8-Br-6-(2-, 3-, and 4-C_5H_4N)	6-H_2N-8-BrC_9H_5N	C_5H_5N	A 5	—	(83)
6-(2,6-$(CH_3)_2$ 3- and 4-C_5H_2N)	6-$H_2NC_9H_6N$	2,6-$(CH_3)_2C_5H_3N$	B-2	12	(87)
3-(4-C_2H_5OOC-2-C_5H_3N)	3 $H_2NC_9H_6N$	4-$C_5H_4NCOOC_2H_5$	A-5	—	(210)
8-(2-, 3-, and 4-(C_5H_4N)-6-(2 C_5H_4N)	8-H_2N-6-(2-C_5H_4N)C_9H_5N	C_5H_5N	A-5	—	(85)
Pyrroles:					
N-C_2H_5OOC 2-C_6H_5	$C_6H_5NH_2$	$C_4H_4NCOOC_2H_5$	B-1	29	(336)
Phthalocyanines:					
(?-$C_5H_4N)_4$	$(H_2N)_4$-phthalocyanine	C_5H_5N	A-5	—	(168)

TABLE 2—*Continued*

Product	Component A	Component B	Method(b)	Yield	Reference
		Ferrocenes			
				per cent	
C_6H_5	$C_6H_5NH_2$	Ferrocene	A-8	65	(54)
			A-6(i)	17	(393)
			B	46	(54)
o-$CH_3C_6H_4$	*o*-$CH_3C_6H_4NH_2$	Ferrocene	A-8	43	(54)
p-$CH_3C_6H_4$	*p*-$CH_3C_6H_4NH_2$	Ferrocene	A-6	57	(306b)
p-HOC_6H_4	*p*-$HOC_6H_4NH_2$	Ferrocene	A-8	14	(54)
			A-6(l)	60	(393)
o-$HOOCC_6H_4$	*o*-$H_2NC_6H_4COOH$	Ferrocene	A-8	7	(54)
			A-6(l)	15	(393)
p-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4NH_2$	Ferrocene	A-8	35	(54)
			A-6	40	(306b)
o-$O_2NC_6H_4$	*o*-$O_2NC_6H_4NH_2$	Ferrocene	A-8	5	(54)
p-$O_2NC_6H_4$	*p*-$O_2NC_6H_4NH_2$	Ferrocene	A-8	18	(54)
			A-6	64	(306b)
			A-6(l)	10	(393)
m-ClC_6H_4	*m*-$ClC_6H_4NH_2$	Ferrocene	A-8	34	(54)
p-$HO_3SC_6H_4$	*p*-$H_2NC_6H_4SO_3H$	Ferrocene	A-8	—	(54)
8-$HOOCC_{10}H_6$	8-H_2N-1-$C_{10}H_6COOH$	Ferrocene	A-6(l)	6	(393)
$(C_6H_5)_2$	$C_6H_5NH_2$	Ferrocene	A-8	9	(54)
			A-6(l)	20	(393)
			B	8	(54)
	$C_6H_5NH_2$	Phenylferrocene	A-8	52	(54)
(*p*-$CH_3OC_6H_4)_2$	*p*-$CH_3OC_6H_4NH_2$	Ferrocene	A-8	7	(54)
			A-6	—	(306b)
(*p*-$O_2NC_6H_4)_2$	*p*-$O_2NC_6H_4NH_2$	Ferrocene	A-6(l)	60	(393)
(*m*-$ClC_6H_4)_2$	*m*-$ClC_6H_4NH_2$	Ferrocene	A-8	0.4	(54)
$(C_6H_5)_3$	$C_6H_5NH_2$	Phenylferrocene	A-8	10	(54)
$(C_6H_5)_5$	$C_6H_5NH_2$	Ferrocene	A-6	42	(306b)
(4-$C_6H_5C_6H_4)_2$	4-$C_6H_5C_6H_4NH_2$	Ferrocene	A-6(l)	50	(393)
(8-$HOOCC_{10}H_6)_2$	8-H_2N-1-$C_{10}H_6COOH$	Ferrocene	A-6(l)	30	(393)

(a) Excepting the products of quantitatively studied arylations recorded in table 4A.

(b) The procedures are designated by letters and numbers:

A-1 = diazohydroxide reaction (NaOH)
A-2 = sodium diazotate procedure
A-3 = sodium acetate modification
A-4 = stabilized diazonium salt procedure
A-5 = pyridine method
A-6 = use of aqueous diazonium salt
A-7 = use of aqueous diazonium chloride + trifluoroacetate ions
A-8 = use of aqueous diazonium salt + acetic acid
A-9 = use of diazonium chloride + aluminum chloride
B = nitrosoacetylamine reaction (not further specified)
B-1 = nitrosoacetylamine reaction (N_2O_3)
B-2 = nitrosoacetylamine reaction (NOCl)
B-3 = nitrosoacetylamine reaction [RONO + $(CF_3CO)_2O$]

(c) Without alkali.

(d) Nitrosated amides of acetic, butyric, and benzoic acids gave the same results.

(e) Isolated as the lactone.

(f) Isolated as the hydroxy compound.

(g) An isomer was also produced.

(h) The 2-isomer comprised 16.6 per cent of the phenylated product.

(i) The 1-phenyl isomer predominated.

(j) Percentage of arylated product rather than of theoretical yield. Smaller amounts of two isomers were present; one was thought to be the 3-phenyl isomer.

(k) The isobutyryl derivative was used.

(l) In strongly acid solution.

15 per cent of dimethylbiphenylamines, mostly 4′,5-dimethyl-2-biphenylamine (299).

A 1-aryl-3,3-dimethyltriazene is more frequently used for generating radicals to attack an aromatic substrate. This kind of triazene is made by coupling an arenediazo compound and dimethylamine. The decomposition of 1,3-bis(4-methoxy-2-nitrophenyl)triazene in benzene gives the expected 4-methoxy-2-nitrobiphenyl, and that of 1-(3,4-dimethylphenyl)-3,3-dimethyltriazene similarly yields 3,4-dimethylbiphenyl (233). The reaction has been used in the study of isomer ratios in the homolytic arylation of toluene, cumene, and *tert*-butylbenzene (342). Either 3,3-dimethyl-1-(3,4,5-trimethoxyphenyl)triazene or the methoxy-free compound arylates methyl 3,4,5-trimethoxybenzoate by displacing a nuclear methoxyl group instead of hydrogen; a methyl 4-aryl-3,5-dimethoxybenzoate is obtained (313). Sometimes the reaction is effected in acid solution; biphenyl was thus obtained in 25–37 per cent yield (131) and 3-nitrobiphenyl in 34–42 per cent yield (252). 3,3-Dimethyl-1-phenyltriazene upon decomposition in nitrobenzene through which hydrogen chloride was bubbled produced a 35 per cent yield of 2- and 4-nitrobiphenyls (131). Perhaps the presence of hydrogen chloride or even acetic acid favors a polar mechanism, but the reactivity of nitrobenzene can hardly be explained on this basis. Under similar conditions 3,3-dimethyl-1-(3-quinolyl)triazene and benzene give the expected 3-phenylquinoline (3).

C. Arylation with other diazo compounds

Diazoanhydrides, $(ArN_2)_2O$, made by careful addition of acetic acid to potassium arenediazotates, react vigorously, even explosively, with aromatic substrates. Arylamines are converted to triazenes, but benzene and toluene yield biaryls, albeit in low yields because of the violence of the reaction. Diazoanhydrides derived from toluene, chlorobenzene, bromobenzene, and nitrobenzene behave thus (23).

The most stable of the diazo ethers, *p*-nitrodiazobenzene methyl ether, upon long boiling with benzene and toluene arylates them to 4-nitrobiphenyl and 4-methyl-4′-nitrobiphenyl, respectively (22).

The decomposition of diazocyanides in nonaqueous media is believed to be homolytic (371). *p*-Chlorobenzenediazocyanide in benzene gave a 1.5 per cent yield of 4-chlorobiphenyl; the ortho isomer gave a 3 per cent yield of 2-chlorobiphenyl, and *p*-bromobenzenediazocyanide gave a 1 per cent yield of 4-bromobiphenyl.

p-Nitrodiazobenzene sulfide, like its oxygen counterpart, the anhydride, yields 4-nitrobiphenyl on reacting with benzene (27).

Potassium benzenediazocarboxylate in refluxing benzene containing bismuth trichloride yields some biphenyl (334). With benzophenone it is reported to produce phenylbenzophenones in 10.5 per cent yield (307).

In the deamination of arenediazonium salts with hypophosphorous acid, some *p*-terphenyl is formed; this must represent radical substitution (5).

D. Arylation with azo compounds

When 1′,1′,1′-triphenylbenzeneazomethane (phenylazotriphenylmethane) was first pyrolyzed in benzene the products were shown (198) to include tetraphenylmethane, biphenyl, and some triphenylmethyl peroxide. The first two compounds could occur by attack on the benzene or by combination of free radicals, and the last by oxidation of the triphenylmethyl radicals. That biphenyl was probably formed through substitution of benzene is indicated by the fact that no biphenyl was found when the decomposition was carried out in chlorobenzene or in nitrobenzene. Some 4-chlorobiphenyl was formed from chlorobenzene, but no biphenyl derivative at all from nitrobenzene. This is not surprising in view of the tendency of triphenylmethyl radicals to attack the nitro group rather than the ring in nitrobenzene (178). Nevertheless, recent work has shown that nitrobiphenyl *can* be obtained in 25 per cent yield (226). Toluene undergoes the same reaction to yield at least 2- and 4-methylbiphenyls (408, 409). Pyridine as substrate has been examined repeatedly; at first only 2- and 4-phenylpyridines were found as arylated products (408, 409), but later the 3-phenyl isomer (3) and a compound that may be either (triphenylmethyl)-phenylpyridine (226) or *p*-2-pyridyltetraphenylmethane (208a) were also characterized. From reaction at 65–70°C. the amounts of isomeric phenylpyridines were 4- > 3- > 2-, whereas at 20°C. (in a much slower process) the order was 3- > 4- > 2- (226). The ratio of the 2-, 3- and 4-phenyl isomers formed at 105°C. was more precisely established (208a) as 29.3–30.6 per cent, 46.4–47.0 per cent, and 23.0–23.7 per cent, respectively. The singularly low proportion of the 2-phenyl isomer in comparison to the relative amounts formed in phenylations of pyridine with diazotized aniline, *N*-nitrosoacetanilide, benzoyl peroxide, lead tetrabenzoate, and phenyl iodosobenzoate is attributed to preferential further substitution of the 2-phenyl isomer by triphenylmethyl radicals and is normal after correction for this (208a).

The photolytic decomposition of 1′,1′,1′-triphenylbenzeneazomethane in benzene apparently follows the same course but has been less investigated (220, 226). A detailed consideration of alternative sequences of reactions, including (*a*) direct decomposition of 1′,1′,1′-triphenylbenzeneazomethane into free radicals, (*b*) a chain or induced decomposition, and (*c*) a "kryptoradical" route in which no truly free radicals occur, resulted in a decision for sequence (a) (226):

$$C_6H_5N{=}NC(C_6H_5)_3 \rightarrow C_6H_5\cdot + N_2 + (C_6H_5)_3C\cdot$$

$$C_6H_5\cdot + ArH \rightarrow C_6H_5Ar + H\cdot$$

$$H\cdot + (C_6H_5)_3C\cdot \rightarrow (C_6H_5)_3CH$$

$$C_6H_5\cdot + (C_6H_5)_3C\cdot \rightarrow (C_6H_5)_4C \text{ (small amount)}$$

The arylation is inhibited in the presence of excess *p*-benzoquinone, which traps the radicals efficiently. Nitric oxide similarly prevents the formation of triphenylmethane by uniting with triphenylmethyl radicals, as does also iodine (in the presence of ethanol, to prevent reversal of the trapping).

Benzenediazoacetate at 20°C. and 1′,1′,1′-triphenylbenzeneazomethane at 50°C. give different relative amounts of biphenyl and phenyldimethylquinoline when they attack a mixture of benzene and dimethylquinoline (226). This was taken to indicate a difference in the phenyl radicals generated, but since such

TABLE 3

Arylations with aroyl peroxides^(a)

Peroxide	Aromatic Substrate	Positions Taken by Aryl Groups	References
Benzoyl	Benzene	Any^(b)	(13, 155, 319, 321, 326)
	Toluene	2, 3, 4	(101, 122, 156)
	Chlorobenzene	2, 3, 4	(13, 101, 105, 234, 341)
	Bromobenzene	2, 3, 4	(105)
	Iodobenzene	2, 3, 4	(105)
	Nitrobenzene	2, 3, 4	(10, 14, 65, 66, 101, 114, 198, 207, 326)
	Phenol	2, 3, 4	(11)
	Methyl benzoate	4	(101)
	Ethyl benzoate	3, 4	(198)
	Biphenyl	2, 3, 4	(157)
	p-Dichlorobenzene	2	(14)
	1,3,5-Trichlorobenzene	2	(14)
	p-Di-*tert*-butylbenzene	2	(66)
	Pyridine	2, 3, 4	(13, 101, 105, 207, 208a, 209, 312)
	Quinoline	4, 5, and others	(209)
	Benzothiazole	2	(305)
p-Chlorobenzoyl	Benzene	Any	(155)
	Pyridine	2, 4	(209)
p-Methoxybenzoyl	Benzene	Any	(209)
	Pyridine	2, 4	(209
o-Nitrobenzoyl	Benzene	Any	(209)
	Pyridine	None	(209)
m-Nitrobenzoyl	Benzene	Any	(209)
	Benzoic acid	3, 4	(209)
	Pyridine	None	(209)
p-Nitrobenzoyl	Benzene	Any	(209)
	Pyridine	None	(209)
o-Carboxybenzoyl	Benzene	None	(209)
	Nitrobenzene	2, 4	(209)
o-Methoxycarbonylbenzoyl	Benzene	Any	(209)
	Pyridine	?	(209)
4-Methoxy-4′-nitrobenzoyl	Benzene	Any	(275)
2-Methoxycarbonyl-4-nitrobenzoyl	Benzene	Any	(209)
2-Methoxycarbonyl-5-nitrobenzoyl	Benzene	Any^(c)	(73, 209)
5-Methoxycarbonyl-2-nitrobenzoyl	Benzene	Any	(73)
2-Methoxycarbonyl-3-nitrobenzoyl	Benzene	Any	(73)
4-Methoxycarbonyl-2-nitrobenzoyl	Benzene	Any	(73)
Phthaloyl . . .	Benzene	Any	(172)
Cinnamoyl	Benzene	(d)	(209)
	Pyridine	(e)	(209)
1-Naphthoyl	Benzene	None	(209)
	Pyridine	?	(209)
2-Naphthoyl	Benzene	Any	(209)
	Pyridine	2, 3, 4	(209)
o-(2-Methyl-6 nitrophenyl)benzoyl	Benzene	Any	(115)

(a) Excepting self-arylations by benzoyl peroxide, which are noted separately, and the quantitatively studied arylations recorded in table 4B.

(b) The products are biphenyl, terphenyls, and quaterphenyls.

(c) The product is a mixture of methyl 4- and 5-nitrobiphenyl-2-carboxylates.

(d) Not strictly arylation; the product is stilbene.

(e) The product is α-stilbazole.

difference is not otherwise observed (13, 14, 119, 208a, 261), the lack of agreement is probably due to the temperature difference (*cf.* 15). The observation that radicals from diazonium salts phenylate ferrocene, whereas those from 1′,1′,1′-triphenylbenzeneazomethane do not, remains unexplained (54). It is possible, but not probable, that this involves the difference between a nonradical and a radical mechanism.

E. Arylation with aroyl peroxides

Studies of the kinetics of thermal decomposition of aroyl peroxides have been extensive and will not be reviewed here. Suffice it to say that both benzoyloxy

TABLE 4

Isomer ratios in arylations

A. With diazo compounds

Product	Component A	Component B	Method[(a)]	Isomer[(b)] 2-	3-	4-	Reference
				per cent	*per cent*	*per cent*	
Nitro-4-methoxybiphenyls.	*p*-$CH_3OC_6H_4NH_2$	$C_6H_5NO_2$	B-1	*45*	*0*	*55*	(360a)
Nitro-*p*-terphenyls	*p*-$C_6H_5C_6H_4NH_2$	$C_6H_5NO_2$	B-1	*54*	*0*	*46*	(144)
Methyl-4-nitrobiphenyls	*p*-$O_2NC_6H_4NH_2$	$C_6H_5CH_3$	B-1	*67*	*0*	*33*	(145)
p-Nitrophenylpyrimidines .	*p*-$O_2NC_6H_4NH_2$	Pyrimidine[(c)]		10	0	14	(281)
Methoxy-4-bromobiphenyls.	*p*-$BrC_6H_4NH_2$	$C_6H_5OCH_3$	A-1	20	0	7	(181)
Methyl-*p*-terphenyls . . .	*p*-$C_6H_5C_6H_4NH_2$	$C_6H_5CH_3$	B-1	*50*	*6*	*44*	(144)
Bromo-*p*-terphenyls	*p*-$C_6H_5C_6H_4NH_2$	C_6H_5Br	B-1	*33*	*15*	*52*	(144)
Nitrobiphenyls	$C_6H_5NH_2$	$C_6H_5NO_2$	A-1	*55–61*	*0 4*	*39–41*	(119)
				12–16	0–1	7–12	
				54 ± 4	*9 ± 2*	*37 ± 4*	(204)
				46	*18*	*36*	(359)
		$C_6H_5NO_2 + C_6H_6$ (1:2)	A-1		*34*	*20*	(359)
		$C_6H_5NO_2$	B	*17*	*23*	*60*	(359)
		$C_6H_5NO_2 + C_6H_6$ (1:2)	B		*22*	*19*	(359)
Chloro-*p*-terphenyls	*p*-$C_6H_5C_6H_4NH_2$	C_6H_5Cl[(d)]	B-1	*32*	*20*	*48*	(144)
(?)′,4-Dinitrobiphenyls	*p*-$O_2NC_6H_4NH_2$	$C_6H_5NO_2$	A-3	*34 ± 5*	*23 ± 3*	*43 ± 3*	(116)
(?)′,3 Dinitrobiphenyls	*m*-$O_2NC_6H_4NH_2$	$C_6H_5NO_2$	A-3	*31 ± 2*	*25 ± 1*	*44 ± 1*	(116)
Methylbiphenyls .	$C_6H_5NH_2$	$C_6H_5CH_3$	B-2	*62*	*20*	*18*	(342)
Chlorobiphenyls	$C_6H_5NH_2$	C_6H_5Cl	A-1	*64*	*22*	*14*	(359)
p-Nitrophenylpyridines	*p*-$O_2NC_6H_4NH_2$	C_5H_5N	A-5	15	5	2	(143)
				24	9	4.5	(183)
Isopropylbiphenyls	$C_6H_5NH_2$	$C_6H_5CH(CH_3)_2$	B-2	*26*	*53*	*21*	(342)
tert-Butylbiphenyls .	$C_6H_5NH_2$	$C_6H_5C(CH_3)_3$	B-2	*15*	*63*	*22*	(342)
Phenylpyridines . .	$C_6H_5NH_2$	C_5H_5N	A-5	*54*	*23*	*23*	(183)
			B-1	*46*	*43*	*11*	(208a)
o-Nitrophenylpyridines	*o*-$O_2NC_6H_4NH_2$	C_5H_5N	A-5	*44.9*	*51.7*	*3.4*	(183)
(?)′,3-Dimethyl-4-nitrobiphenyls . . .	3-CH_3-4-$O_2NC_6H_3NH_2$	$C_6H_5CH_3$	A-3	*82*	*17*	*0*	(415)
				9.5	2	0	
				1-	2-		
Phenylnaphthalene	$C_6H_5NH_2$	$C_{10}H_8$	A-9	*90*	*10*		(297)
			B	*84*	*16*		(227)
(?)-Phenyl-2-ethoxynaphthalene . . .	$C_6H_5NH_2$	2-$C_2H_5OC_{10}H_7$	B	17.1 of 1- 3.1 of 3- 2.3 of 6-			(227)

TABLE 4—*Continued*

B. With benzoyl peroxides

Product	Substrate	Isomer[e]			Reference
		2-	3-	4-	
		per cent	*per cent*	*per cent*	
Nitrobiphenyls	$C_6H_5NO_2$	*46.3*	*0.7*	*53*	(204)
		72	*2*	*26*	(119)
		58	*10*	*32*	(13)
		59.5 ± 4	*8.5 ± 2,* *11.5 ± 2*	*32.4 ± 4,* *29 ± 4*	(11)
		56	*16*	*28*	(208)
Cyanobiphenyls	C_6H_5CN	*60*	*10*	*30*	(103)
Biphenylcarboxylic acids	C_6H_5COOH	*59*	*15*	*26*	(104)
		40[f]	*20*[f]	*31*[f]	
Terphenyls	$C_6H_5C_6H_5$	*48.5*	*23.0*	*28.5*	(65)
α-Trifluoromethylbiphenyls	$C_6H_5CF_3$	*18*	*40*	*42*	(106)
Ethylbiphenyls	$C_6H_5C_2H_5$	*60*	*25*	*25*	(107)
Methoxybiphenyls	$C_6H_5OCH_3$	*67*	*18*	*15*	(374)
Methylbiphenyls	$C_6H_5CH_3$	*65*	*19*	*16*	(107)
		64	*20*	*16*	(342)
		70.8	*16.7*	*12.4*	(207)
α-Trichloromethylbiphenyls	$C_6H_5CCl_3$	*0*	*60*	*40*	(106)
Chlorobiphenyls	C_6H_5Cl	*62 2*	*24.0*	*13.8*	(14)
		64	*23*	*13*	(103)
Bromobiphenyls	C_6H_5Br	*48.5*	*33.0*	*18.5*	(103)
		49.3	*33.3*	*17.4*	(10)
Iodobiphenyls	C_6H_5I	*51.7*	*31.6*	*16.7*	(10)
Fluorobiphenyls	C_6H_5F	*54.1*	*30.7*	*15.2*	(10)
Phenylpyridines	C_5H_5N	*64.3*	*0*	*35.7*	(312)
		58	*28*	*14*	(104)
		54	*32*	*14*	(208a)
Isopropylbiphenyls	$C_6H_5CH(CH_3)_2$	*10*	*60*	*30*	(107)
		29	*50*	*21*	(342)
Methyl biphenylsulfonates	$C_6H_5SO_3CH_3$	*53*	*33*	*14*	(103)
tert-Butylbiphenyls	$C_6H_5C(CH_3)_3$	*24*	*49*	*27*	(66)
		17	*61*	*22*	(342)
biphenyls[g]	$C_6H_5CCl_3$	*0*	*85*	*17*	(106)
iphenyls[h]	$C_6H_5CCl_3$	*0*	*100*	*0*	(106)

[a] The system used for designating the methods used is explained in footnote (b) of table 2.

[b] The numbers set in italics indicate the relative amounts of arylated products rather than the theoretical yields. For any given combination of components A and B, the isomer percentage values are arranged in increasing order of the ratio of the 3-isomer to the 4-isomer.

[c] Statistically there are twice as many chances of forming 4-monosubstituted pyrimidines as 2-monosubstituted products.

[d] Bromobenzene by method A-1 or B gives isomers in the agreeing ratio (qualitative only) ortho > meta > para (360).

[e] All the numbers are given in italics and indicate the relative amounts of arylated products only and not the theoretical yields. For any given substrate, the isomer products are arranged in increasing order of the ratio of the 3-isomer to the 4-isomer.

[f] In the presence of pyridine.

[g] Made with *p*-chlorobenzoyl peroxide.

[h] Made with *p*-nitrobenzoyl peroxide.

and aryl radicals are usually produced; decarboxylation and consequent formation of aryl radicals are favored by increase in temperature. These conclusions from rates of reaction are borne out by preparative work, in which benzoyloxylation is preferred at lower temperatures (321) and with especially reactive aromatic nuclei (102, 341). Table 3 presents a literature summary of all such arylations except self-arylations. These occur, often as minor reactions, when benzoyl peroxide is heated in various solvents. The formation of *o*- and *p*-phenylbenzoic acids in this way has been noted in acetic acid (164) and alkylbenzenes (107, 156, 207). *p*-Phenylbenzoic acid alone has been identified more frequently among products of reaction in 2,2,4-trimethylpentane (209), 1,2-dichloroethane (329), 1,1,2,2-tetrachloroethane (329), 2-methyl-1-propanol (158), 2,3-butanediol (208), acetic acid (158, 159), diethyl malonate (375), cyclohexane (160), cyclopropyl methyl ketone (180), phenylcyclopropane (180), and pyridine (105, 312). Recently the pyrolysis of acyl peroxides of the form $C_6H_5CO_2OCO(CH_2)_nCOOR$ has also been shown to yield *p*-phenylbenzoic acid (167).

Because arylation with aroyl peroxides is cleaner than arylation with diazo compounds, it has been preferred as a way for studying competition between nuclear positions (orientation) and between molecules (relative reactivities). The results of the former are summarized in table 4 and interpreted in the accompanying paper (15). The Ingold (235) competitive method for comparing rates of reaction is being applied systematically and successfully in several laboratories. The topic has been reviewed recently (199, 201, 211) and further theoretical treatment is presented by Augood and Williams (15).

F. Arylation with metalloörganic compounds

It has been postulated (257) that aryl radicals are involved when halogen atoms of aryl halides are displaced by the action of Grignard reagents in the presence of organic halides and metal salts. Certainly the formation of terphenyls, quaterphenyls, and probably higher polyphenyls constitutes substitution under the current definition. When butylmagnesium bromide was decomposed in the presence of chlorobenzene and cobaltous chloride, biphenyl was produced in only 3 per cent yield, but there was an 11 per cent yield of polyphenyls (262). Similarly, phenylaluminum diiodide and bromobenzene heated in benzene generate biphenyl, terphenyls, quaterphenyls, and quinquephenyls (388, 390).

Phenylmagnesium bromide when sufficiently heated in toluene causes phenylation in the 4-position; *o*-xylene is substituted in an undetermined position, probably the 4-position also (258) (*cf.* page 81). In chlorobenzene the decomposition of phenylmagnesium bromide gave chlorobiphenyl in 5 per cent and biphenyl in 39 per cent yield. Obviously the high reactivity of Grignard reagents toward most functional groups prevents much extension of this work. Similarly, the known arylation of pyridines and quinolines by these reagents probably involves a polar, additive route instead of a radical mechanism.

The photochemical decomposition of phenylmercuric hydroxide in toluene produces methylbiphenyls among other products (330), and that of diphenylmercury in bromobenzene produces 4-bromobiphenyl (327). Free phenyl radicals are thought to be responsible for the ortho and para phenylation of ethyl benzoate when that liquid is used as solvent during the Ullmann treatment of iodobenzene with copper (324). The same radicals from diphenyliodonium chloride heated with pyridine and sodium hydroxide (344), or from phenyl iodosobenzoate with pyridine (208a), give 2-, 3-, and 4-phenylpyridines.

When lead tetrabenzoate is decomposed at low temperatures the reaction does not appear to involve free radicals (208) and aromatic substitution does not occur. However, at higher temperatures radical substitutions of chlorobenzene and nitrobenzene produce mixtures of isomeric chlorobiphenyls and of isomeric nitrobiphenyls. Under the same conditions, the reactions of lead tetrabenzoate and of benzoyl peroxide with nitrobenzene yield almost identical ratios of isomers (208).

It appears that aryl radicals are involved in the decomposition of silver iodide dibenzoate in chlorobenzene at 130°C., which produces chlorobiphenyls (22 per cent), *p*-chlorophenyl benzoate, benzoic acid, and silver iodide (58). Reaction with nitrobenzene produces nitrobiphenyls and *m*-nitrophenyl benzoate. It seems not improbable that silver benzoate itself may phenylate aromatic nuclei.

Somewhat similarly, heating a solution of *tert*-butyl peroxide and triphenylsilane in chlorobenzene forms *o*- and *p*-chlorobiphenyls, along with triphenylchlorosilane (96).

G. Other intermolecular arylations

The rearrangement of benzyl phenyl ethers (212, 213) in quinoline, as already noted (page 81) produces hydroxyphenylquinolines, evidently by way of the mesomeric phenoxy radical.

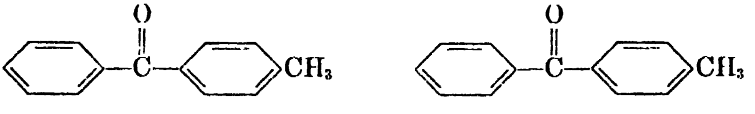
Besides the hydroxylation of benzene by Fenton's reagent (368), water irradiated with x-rays (368), or gaseous oxygen (217) (see page 101), these reagents cause some formation of *p*-terphenyl (368). Indeed, the decomposition of individual compounds by radiation often leads to the formation of radicals which can arylate the original material or some new substance formed. This kind of process has been reviewed exhaustively for aromatic hydrocarbons (128) and somewhat earlier for all classes of aromatic compounds (230). The field is an extensive one, and its treatment here is restricted by the arbitrary exclusion of the coupling of like nuclei, e.g., the benzene–biphenyl conversion, from consideration. Nevertheless, a few examples of substitutions of this type will be given.

Benzene has repeatedly been shown to yield about equal amounts of *m*-terphenyl and *p*-terphenyl (besides, of course, many other products) when subjected to high temperatures; the absence of the ortho isomer is probably due to steric effects. Upon prolonged exposure to red heat, phenol yields *p*-hydroxybiphenyl (293). The pyrolysis of benzoic acid yields some phenylbenzoic acids, ana methyl benzoate gives methyl *m*-phenylbenzoate and methyl *p*-phenylbenzoate (230); again the orientation is noteworthy.

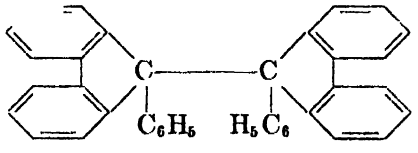
IV. INTRAMOLECULAR ARYLATION

The pyrolysis of cyclic diazoamino compounds, i.e., benzotriazoles, has long been known to yield carbazoles (80, 227, 253, 384), but the subject has already been adequately reviewed (348). Carbazoles are obtained also from diazotized *N*-alkyl-*N*-aryl- and *N*,*N*-diaryl-*o*-phenylenediamines, which cannot yield triazoles as intermediates (125, 320, 373). The Pschorr synthesis of phenanthrenes is recognizable as a counterpart of the Gomberg preparation of biaryls and thus deserves attention, but again an extensive bibliography and studies of modifications of the reaction have been made recently (186, 187, 188, 203, 205, 206, 347).

Of especial interest is the discovery of evidence for internuclear chain transfer within molecules. In the course of investigations of radical intermediates (118, 332), 2-benzoyl-*N*-nitrosoacetanilide in benzene was found to react to give 15 per cent of 2-phenylbenzophenone and 7 per cent of fluorenone, as might be expected. However, decomposition in carbon tetrachloride of the diazonium fluoborate derived from 2′-amino-4-methylbenzophenone gave not only 10 per cent of 3-methylfluorenone and 10 per cent of 2′-chloro-4-methylbenzophenone but also 10 per cent of 2-chloro-4-methylbenzophenone. The last-named product would appear to be formed only as the result of a transfer of radical status from one nucleus within the molecule to the other. Evidence for this type of product was not found in heterolytic reactions under acid conditions, but it was also obtained in the Sandmeyer reaction using cuprous bromide. It seems clear that the Sandmeyer reaction also proceeds at least in part by a course which allows for some intramolecular transfer substitution:

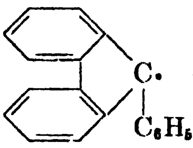


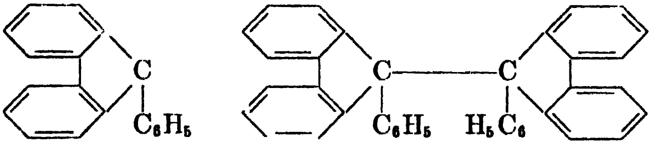
The disproportionation of triphenylmethyl free radicals involves ortho attack to cause cyclization. For cyclization of triphenylmethyl on long standing in most organic solvents in diffuse light (50, 351) the overall reaction is

$3[(C_6H_5)_3C]_2 \rightarrow 4(C_6H_5)_3CH +$ 

which takes place stepwise (50, 276) as follows:

$$3[(C_6H_5)_3C]_2 \rightleftarrows 6(C_6H_5)_3C\cdot$$

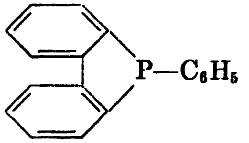
$6(C_6H_5)_3C\cdot \xrightarrow{\text{photochemical, slow}} 2$  $+ \; 4(C_6H_5)_3CH$



In alkaline dioxane the products are 9-phenylfluorene and triphenylmethane (276).

Correspondingly, 9-phenylfluorene and ammonia are among the products of the pyrolysis of 1,2-bis(triphenylmethyl)hydrazine in the presence of anhydrous zinc chloride. They are produced also in the reaction of triphenylmethylamine with zinc chloride (372); this observation suggested that the same amine is an intermediate in the first reaction. The belief that radicals are involved is strengthened by the observation that phenol is formed when the hydrazine is heated in air or oxygen, but not in carbon dioxide. The triphenylmethyl radical appears to participate in all of these reactions.

Evidently related is the decomposition of pentaphenylphosphorus (416) to form benzene, biphenyl, triphenylphosphine, and *o*-diphenylenephenylphosphine.



V. AMINATION

The direct substitution of an amino group in an aromatic nucleus by a radical sequence is not common. The action of the imino radical, generated by irradiation of hydrazoic acid, on liquid toluene or nitrobenzene gives traces of primary arylamines (254), but the substitution fails for benzene vapor (335). However, benzene and ammonia give aniline in 28 per cent yield, besides many byproducts, when subjected to a silent electrical discharge (376). Reducing agents acting upon hydroxylamine in acid solution generate the free amino radical, which can substitute in benzene or toluene by way of an addition compound barely stable enough to be isolated (110, 357).

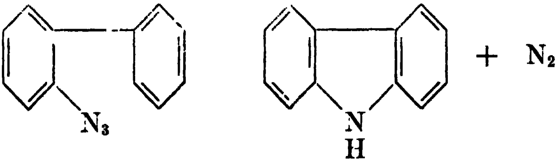
$$HONH_3^+ + Ti^{3+} \rightarrow H_2N\cdot + Ti^{4+} + H_2O$$

$$H_2N\cdot + C_6H_6 \rightarrow H_2NC_6H_6\cdot$$

$$H_2NC_6H_6\cdot \rightarrow \text{a primary arylamine } \textit{inter alia}$$

The reaction is comparable to hydroxylation by means of Fenton's reagent.

Independently binuclear aromatic compounds containing an azido group in the position ortho to a linking bond are sterically well suited to ring closure. Thermal or photochemical decomposition of *o*-azidobiphenyls gives carbazoles in excellent yields except when the azido group is flanked by a nitro group (365):



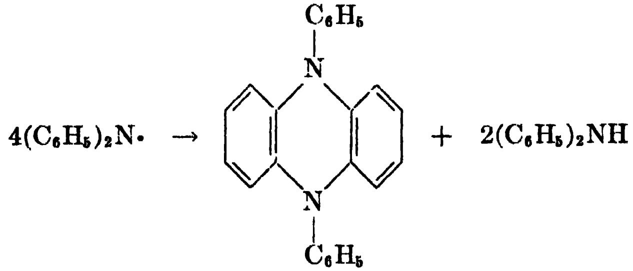
The reaction succeeds also for 2-(*o*-azidophenyl)thiophene and 3-(*o*-azidophenyl)-pyridine but fails for 2-(*o*-azidophenyl)pyridine, 1-azidonaphthalene (364), and 2,2′-diazidobiphenyl (366). When the two nuclei are separated by one other atom, Y, the cyclization is normal for Y = —S— and —SO_2— but not for Y = —O—, —N($COCH_3$)—, or —CO— (366).

Although there is considerable evidence of the generation of phenylimino radicals, C_6H_5N:, by the pyrolysis of azidobenzene or phenylhydroxylamine, such radicals do not affect benzene or nitrobenzene and attack *p*-xylene only in a side chain (45, 343). Only by heating *p*-azidotoluene in phenol at 160°C. has substitution been accomplished (24).

$$p\text{-}CH_3C_6H_4N_3 + C_6H_5OH \rightarrow 4\text{-}(p\text{-}CH_3C_6H_4NH)C_6H_4OH + N_2$$

p-Anilination of aromatic compounds has been effected with azidobenzene and aluminum chloride and even assigned a radical course (49), but a polar route seems at least as likely.

To be mentioned here are the remarkable thermal disproportionations of diarylamino radicals, since further ring substitution is involved. They are illustrated for the diphenylamino radical (406):



5,10-Dihydro-5,10-diphenylphenazine

$$2(C_6H_5)_2N\cdot \rightarrow o\text{-}C_6H_5NHC_6H_4N(C_6H_5)_2$$

The action of certain mild reducing agents, notably potassium ferrocyanide or cuprous ion, upon aqueous diazonium salts leads in part to arylazo-substituted aromatic compounds. This has been tentatively represented as involving the arylazo radical:

(a) $C_6H_5N_2^+ + e^- \rightarrow C_6H_5N_2\cdot$

(b) $C_6H_5N_2\cdot \rightarrow C_6H_5\cdot + N_2$

(c) $C_6H_5\cdot + C_6H_5N_2^+ \rightarrow C_6H_5C_6H_4N_2^+ + H\cdot$

(d) $C_6H_5\cdot + C_6H_5C_6H_4N_2^+ + e^- \rightarrow C_6H_5C_6H_4N{=}NC_6H_5$

(e) $C_6H_5\cdot + \text{H source} \rightarrow C_6H_6$

(f) $C_6H_5N_2\cdot + C_6H_6 \rightarrow C_6H_5N{=}NC_6H_5 + H\cdot$

Equations (c) and (d) are supposed to explain the observed formation of arylazobiaryls (142, 346). Equation (d) is essentially that recently preferred over combination of $ArN_2\cdot$ and $Ar\cdot$ to account for the production of a little azobenzene from benzenediazonium salts decomposed in acetate-buffered methanol (120). Substitution by the arylazo radical (equation (f)) (217) appears rather unlikely. To explain the observed formation of azobenzene-2-carboxylic acid from a diazotized mixture of aniline and anthranilic acid, it is necessary only to postulate that the dipolar-ion form of the 2-carboxybenzenediazonium salt is sufficiently stabilized as such to await attack by phenyl radicals as in equation (d).

$$o\text{-}^{-}OOCC_6H_4N_2^+ + C_6H_5\cdot + e^- \rightarrow o\text{-}^{-}OOCC_6H_4N{=}NC_6H_5$$

VI. AMIDATION, INCLUDING SULFONAMIDATION

A. Amidation

There are only two examples of formation of *N*-aryl carboxamides by radical substitution. The radicals generated from benzoyl azide do not attack benzene, even in the presence of triphenylmethyl (316), but *N*-bromosuccinimide acting upon acridine yields among other products 9-succinimidoacridine, several of its bromo derivatives, and probably a disuccinimidoacridine (349). Similarly, the succinimido radical from *N*-bromosuccinimide does produce a little *N*-phenylsuccinimide in the presence of olefins (225).

B. Sulfonamidation

When aromatic sulfonyl azides are heated in various aromatic liquids the ensuing reaction is not a typical Curtius rearrangement (97). On the contrary, the nature of the compounds that can be isolated from the reaction mixtures after cessation of nitrogen evolution, which begins at approximately 100°C., shows that substitution of the aromatic liquid occurs in nearly every case. The isolable products consist primarily of simple and *N*-arylated arenesulfonamides. The reactions can be conceived as follows, (b) and (c) being alternatives:

(a) $ArSO_2N_3 \rightarrow ArSO_2N\colon + N_2$

(b) $ArSO_2N\colon + Ar'H \rightarrow ArSO_2NHAr'$

(c) $ArSO_2N\colon + 2Ar'H \rightarrow ArSO_2NH_2 + 2Ar'\cdot$

The fate of the free aryl radicals in (c) is not clear. A benzidine was believed formed when aniline was used as the aromatic substrate (105), but the compound could not be fully characterized.

The results of an extensive series of experiments on sulfonamidation are reviewed in table 5. They are corrected by later work only for pyridine and quinoline. It was suggested (4) and soon confirmed (9, 59, 108) that the compounds earlier supposed to be *N*-pyridylarenesulfonamides in fact constitute a remarkable kind of dipolar compound, $C_5H_5\overset{+}{N}{-}\overset{-}{N}SO_2Ar$, and that *C*-sulfonamidation of the pyridine nucleus does not occur. The *N*-(*N*-pyridyl)arenesulfonimides so obtained can even be hydrolyzed to *N*-iminopyridine, but this substance is very short-lived (108). Thus the decomposition of sulfonyl azides in pyridine (and by analogy, in quinoline) is like the conversion of tertiary amines to amine oxides.

$$R_3N + [O] \rightarrow R_3NO$$

$$R_3N + ArSO_2N\colon \rightarrow R_3NNSO_2Ar$$

A systematic investigation of the ratios of isomeric benzenesulfonanilides produced by the thermal decomposition of benzenesulfonyl azide in selected mono-

TABLE 5

Sulfonamidations with sulfonyl azides (97)

A. Normal reaction of type (b)[a]; isomers not possible or not specified

$C_6H_5SO_2N_3 + C_6H_6, C_6H_5CH_3, C_6H_5NH_2, C_6H_5NHCH_3, C_6H_5N(CH_3)_2, (C_6H_5)_2NH$
$p\text{-}CH_3C_6H_4SO_2N_3 + C_6H_6, p\text{-}C_6H_4(CH_3)_2, C_6H_5NH_2, C_6H_5NHCH_3$
$p\text{-}ClC_6H_4SO_2N_3 + p\text{-}C_6H_4(CH_3)_2$
$1,3\text{-}C_6H_4(SO_2N_3)_2 + p\text{-}C_6H_4(CH_3)_2$
$p\text{-}CH_3CONHC_6H_4SO_2N_3 + p\text{-}C_6H_4(CH_3)_2$
$1\text{-}C_{10}H_7SO_2N_3 + p\text{-}C_6H_4(CH_3)_2$
$2\text{-}C_{10}H_7SO_2N_3 + p\text{-}C_6H_4(CH_3)_2, C_6H_5NHCH_3, C_6H_5N(CH_3)_2$
$1,5\text{-}C_{10}H_6(SO_2N_3)_2 + p\text{-}C_6H_4(CH_3)_2$
2-Anthraquinonesulfonyl azide + $p\text{-}C_6H_4(CH_3)_2$

B. Normal reaction of type (b)[a]; orientation as noted

$C_6H_5SO_2N_3 + C_6H_5CH_3 \rightarrow$ 2.4 ortho: no meta: 1 para
$C_6H_5SO_2N_3 + C_6H_5N(CH_3)_2 \rightarrow$ 1 ortho: 2 para
$p\text{-}CH_3C_6H_4SO_2N_3 + C_6H_5N(CH_3)_2 \rightarrow$ ortho only
$p\text{-}CH_3C_6H_4SO_2N_3 + C_6H_5NH_2$ or $C_6H_5NHCH_3$ or $C_6H_5N(CH_3)_2 \rightarrow$ ortho only
$p\text{-}CH_3C_6H_4SO_2N_3 + C_{10}H_8 \rightarrow$ 1-isomer only
$2\text{-}C_{10}H_7SO_2N_3 + C_6H_5NH_2 \rightarrow$ ortho only
$2\text{-}C_{10}H_7SO_2N_3 + C_{10}H_8 \rightarrow$ 1-isomer only

C. Failure of normal reactions; (c)[a] may occur, but no sulfonamidation

$C_6H_5SO_2N_3 + C_6H_5CHO, C_6H_5NO_2$, pyridine,[a][b]
$p\text{-}CH_3C_6H_4SO_2N_3$ + pyridine[a][b]
$1,3\text{-}C_6H_4(SO_2N_3)_2 + C_6H_5N(CH_3)_2$
$2\text{-}C_{10}H_7SO_2N_3$ + pyridine,[a][b] quinoline[a][b]

[a] See text

[b] From results of later work.

TABLE 6

Isomer ratios in sulfonamidation at 105–115°C.

Aromatic Substrate	Average Ratio of Isomeric Anilines[a]			Aromatic Substrate	Average Ratio of Isomeric Anilines[a]		
	Ortho	Meta	Para		Ortho	Meta	Para
Toluene	60	12	28	Anisole	49	21	30
Chlorobenzene	56	15	29	Phenol	58	20	22
Bromobenzene	57	10	33				

[a] Produced by hydrolysis of the sulfonanilides.

substituted benzenes (113) gave the results shown in table 6. Benzonitrile, benzoyl chloride, and methyl benzoate gave mixed crystalline products of sulfonamidation, but the results as regards isomer ratio were indecisive. No such sulfonamide could be isolated from the reaction mixture made with nitrobenzene. However, nitric oxide was evolved, presumably from attack on the nitro group by the benzenesulfonimino radical.

The behavior of arenesulfonyl azides toward aromatic substrates suggested trial of sulfuryl azide. The analogy fails, however; in an amazing and surely very complex process, sulfuryl azide and benzene yield pyridine (99, 352, 353). Carbonyl azide with benzene acts similarly.

VII. HYDROXYLATION

A. Hydroxylation with hydrogen peroxide

While benzene can be hydroxylated in aqueous solution or suspension by hydrogen peroxide alone (43), better results are obtained with Fenton's reagent (hydrogen peroxide and a ferrous salt). Oxidations of this type have been reviewed recently (40a, 385). The reagent generates hydroxyl radicals by the reaction

$$Fe^{2+} + HOOH \rightarrow Fe^{3+} + OH^- + HO\cdot$$

and these readily hydroxylate aromatic nuclei. It has been supposed that the process is not a chain reaction (290) but in the presence of much ferric ion the process goes by the following steps:

$$\text{(a)} \quad ArH + HO\cdot \rightarrow Ar\cdot + H_2O$$

$$\text{(b)} \quad Fe^{3+} + H_2O + Ar\cdot \rightarrow ArOH + Fe^{2+} + H^+$$

(and *not* $Ar\cdot + HO\cdot \rightarrow ArOH$)

$$\text{(c)} \quad Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + HO\cdot$$

These constitute a chain mechanism for transfer substitution (41, 42). Biaryl formation evidently competes with hydroxylation, and so does reconversion to the substrate (41, 290).

$$\text{(d)} \quad Ar\cdot + Ar\cdot \rightarrow ArAr$$

$$\text{(e)} \quad Ar\cdot + Fe^{2+} + H^+ \rightarrow ArH + Fe^{3+}$$

In air or oxygen biaryl formation is suppressed entirely (41, 368); otherwise the primary products are phenols and biaryls. The ability of ferric ions to promote aromatic hydroxylation had been noted before (7, 370). Cupric ions are even more effective for oxidizing phenyl radicals to phenol (42, 268).

Since phenols themselves are readily further substituted, hydroxylation usually gives mixtures; thus phenol itself goes to pyrocatechol and hydroquinone (283, 285). A further complication is the well-known tendency of ferric ions to form complexes with phenols; this can be minimized by adding fluoride or pyrophosphate ions to remove ferric ions (41, 370).

The complications due to iron can be avoided by generating hydroxyl radicals merely by the photolysis of aqueous hydrogen peroxide. The ratio of phenol to biphenyl is then nearly independent of the concentrations of hydrogen peroxide and benzene and of the light intensity, but is greatly increased by decreasing the pH to about 1. These observations are not yet explained (40a).

B. Hydroxylation with irradiated water

Vigorous irradiation of water also produces hydroxyl radicals

$$H_2O(l) \rightsquigarrow H\cdot + HO\cdot$$

L 7 9 8 9

TABLE 7

Hydroxylations with water or hydrogen peroxide

<table>
<tr><th>Aromatic Substrate</th><th colspan="5">Product[a]</th><th>Source of Hydroxyl[b]</th><th>References</th></tr>
<tr><td>C_6H_6</td><td colspan="5">C_6H_5OH</td><td>I</td><td>(41, 95, 291, 311)</td></tr>
<tr><td></td><td colspan="5"></td><td>II</td><td>(268)</td></tr>
<tr><td></td><td colspan="5"></td><td>III</td><td>(111, 147, 367, 368, 382)</td></tr>
<tr><td></td><td colspan="5"></td><td>IV</td><td>(367, 369)</td></tr>
<tr><td></td><td colspan="5"></td><td>V</td><td>(42)</td></tr>
<tr><td></td><td colspan="5"></td><td>VII</td><td>(88, 294, 295)</td></tr>
<tr><td></td><td colspan="5">o-$C_6H_4(OH)_2$</td><td>I</td><td>(95)</td></tr>
<tr><td></td><td colspan="5"></td><td>IV</td><td>(367, 369)</td></tr>
<tr><td></td><td colspan="5">p-$C_6H_4(OH)_2$</td><td>IV</td><td>(369)</td></tr>
<tr><td>$C_6H_5CH_3$</td><td colspan="5">$CH_3C_6H_4OH$ isomers</td><td>I</td><td>(291)</td></tr>
<tr><td></td><td colspan="5"></td><td>VII</td><td>(294)</td></tr>
<tr><td>C_6H_5Cl</td><td colspan="5">Ortho meta para isomers of ClC_6H_4OH</td><td>I</td><td>(291)</td></tr>
<tr><td></td><td colspan="5">*40–45%* *20–25%* *20–25%*</td><td>All I</td><td>(248)</td></tr>
<tr><td></td><td colspan="5">*25–30%* *20–30%* *40–45%*</td><td>All III</td><td>(248)</td></tr>
<tr><td>$C_6H_5NO_2$</td><td colspan="5">Ortho meta para isomers of $O_2NC_6H_4OH$</td><td>I</td><td>(291)</td></tr>
<tr><td></td><td colspan="5">*25–30%* *20–25%* *50–55%*</td><td>All I</td><td>(278)</td></tr>
<tr><td></td><td colspan="5">*28–36%* *27–31%* *34–45%*</td><td>All III at pH 2–12</td><td>(279)</td></tr>
<tr><td>C_6H_5OH</td><td colspan="5">o-$C_6H_4(OH)_2$ and p-$C_6H_4(OH)_2$ only, in following ratios:</td><td></td><td></td></tr>
<tr><td></td><td colspan="5">*90:10*</td><td>I, Fe^{3+} only</td><td>(370)</td></tr>
<tr><td></td><td colspan="5">*70:30*</td><td>I, no addition</td><td>(78, 166, 284, 285, 370)</td></tr>
<tr><td></td><td colspan="5">*30:70*</td><td>I, NaF addition</td><td>(356)</td></tr>
<tr><td></td><td colspan="5">*65–80:20–35*</td><td>III, pH 2–12</td><td>(370)</td></tr>
<tr><td></td><td colspan="5">1,2,3-$C_6H_3(OH)_3$</td><td>I</td><td>(166)</td></tr>
<tr><td>$C_6H_5OCH_3$</td><td colspan="5">o-$CH_3OC_6H_4OH$</td><td>I</td><td>(284)</td></tr>
<tr><td>$C_6H_5CONH_2$</td><td colspan="5">o-$HOC_6H_4CONH_2$</td><td>I</td><td>(291)</td></tr>
<tr><td>m-$CH_3C_6H_4COOH$</td><td colspan="5">x-HO 3-$CH_3C_6H_3COOH$</td><td>V</td><td>(36)</td></tr>
<tr><td>p-$CH_3C_6H_4COOH$</td><td colspan="5">2-HO-4-$CH_3C_6H_3COOH$</td><td>V</td><td>(35, 36)</td></tr>
<tr><td>o-HOC_6H_4COOH</td><td colspan="5">2,5-$(HO)_2C_6H_3COOH$</td><td>I</td><td>(52, 304)</td></tr>
<tr><td></td><td colspan="5"></td><td>VI</td><td>(52)</td></tr>
<tr><td>p-HOC_6H_4COOH</td><td colspan="5">3,4-$(HO)_2C_6H_3COOH$</td><td>I</td><td>(52)</td></tr>
<tr><td></td><td colspan="5"></td><td>VI</td><td>(52)</td></tr>
<tr><td>$C_6H_5SO_3H$</td><td colspan="5">o- and/or p-$HOC_6H_4SO_3H$</td><td>I</td><td>(291)</td></tr>
<tr><td>Coumarin</td><td colspan="5">Umbelliferone</td><td>I</td><td>(52)</td></tr>
<tr><td>o-$HOOCC_6H_4CH{=}CHCOOH$</td><td colspan="5">x HO-2-$HOOCC_6H_3CH{=}CHCOOH$</td><td>I</td><td>(52)</td></tr>
<tr><td></td><td colspan="5"></td><td>VI</td><td>(52)</td></tr>
<tr><td>$C_{10}H_8$</td><td colspan="5">1-$C_{10}H_7OH$ (*80%*) and 2 $C_{10}H_7OH$ (*20%*)</td><td>I</td><td>(52)</td></tr>
<tr><td></td><td colspan="5"></td><td>VI</td><td>(52)</td></tr>
<tr><td></td><td colspan="5">$C_{10}H_7OH$</td><td>VII</td><td>(294)</td></tr>
<tr><td>C_6H_5COOH</td><td colspan="3">HOC_6H_4COOH</td><td colspan="2">$(HO)_2C_6H_3COOH$</td><td></td><td></td></tr>
<tr><td></td><td>o-</td><td>m-</td><td>p-</td><td>2,5-</td><td>3,4-</td><td></td><td></td></tr>
<tr><td></td><td>I (52, 291)</td><td></td><td>I (52, 367, 368)</td><td>I (52)</td><td>I (52)</td><td></td><td></td></tr>
<tr><td></td><td>II (268)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>III (111, 368)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>*30%*</td><td>*10%*</td><td>*60%*</td><td></td><td></td><td>All III</td><td>(280)</td></tr>
<tr><td></td><td>*40%*</td><td>*40%*</td><td>*20%*</td><td></td><td></td><td>All V</td><td>(35, 36)</td></tr>
<tr><td></td><td>*33%*</td><td>*17%*</td><td>*17%*</td><td>*7%*</td><td>*24%*</td><td>All VI</td><td>(52)</td></tr>
</table>

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[a] Percentage yields in italics refer not to efficiency of conversion of substrate but to ratio of products, usually isomers, shown in the same horizontal line. Efficiencies of conversion are neglected because the reaction is of little or no preparative value.

[b] The Roman numerals designate methods as follows:

I = Fenton's reagent
II = $H_2O_2 + Cu^{++}$
III = H_2O + x-rays or gamma rays alone
IV = H_2O + neutrons or alpha particles
V = H_2O + ultraviolet light + Fe^{3+}
VI = H_2O_2 + ultraviolet light
VII = H_2O_2 in $R_3COH + V_2O_5$, CrO_3, or OsO_4

without limiting the pH range as the Fenton method does. It has been shown both theoretically and experimentally that the reaction of ArH and HO•, whether by way of an adduct or not, is very much more likely to yield Ar• + H_2O —that is, to react by transfer substitution—than H• + ArOH. Phenols are then formed from Ar• and HO•, and biaryls from 2Ar•; the reaction

$$\mathrm{Ar\cdot + ArH \rightarrow ArAr + H\cdot}$$

is less probable, since the yield of biaryl is sometimes independent of the concentration of ArH (42, 368). Neutrons and α-particles give somewhat more energetic attack than x-rays and gamma rays, and more polyphenols and ring-cleavage products are formed (369).

In general there is good agreement among isomer ratios for the several hydroxylations of the same substrate (see table 7). An exception is the production of hydroxybenzoic acids from aqueous benzoic acid, which has given the ortho-meta-para ratio 5:2:10 with x-rays (280), 2:2:1 with ultraviolet light in the presence of ferric ions (35, 36), and 2:1:1 with hydrogen peroxide irradiated with ultraviolet light (52). These determinations were very approximate, and perhaps better agreement may be obtained in the future.

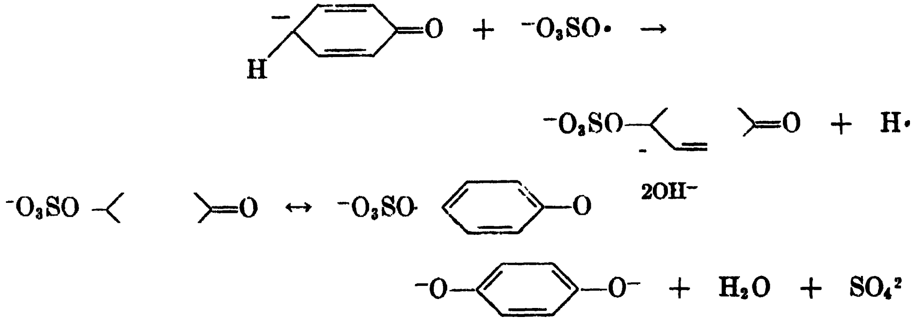
The formation of *o*-nitrosophenols from aromatic substrates, air or hydrogen peroxide, and hydroxylamine (37, 38, 39, 94) or sodium nitroprusside (40) is probably the result of hydroxylation and then nitrosation (269).

Tetralin hydroperoxide does not hydroxylate an aromatic nucleus, even so susceptible a one as *m*-dinitrobenzene (338), but it might do so in the presence of a reducing ion such as Fe^{+2} or Cu^{+1}.

C. Hydroxylation with peroxy acids

The Elbs alkaline persulfate oxidation of monohydric phenols to dihydric phenols, which has been lately reviewed (358), may well proceed by a radical mechanism. The radical-ion $^{-}O_3SO\cdot$ is supposed to attack the phenoxide anion, although such an anion–anion approach seems unlikely.

$$\mathrm{Fe^{2+}\ (trace) + S_2O_8{}^{2-} \rightarrow Fe^{3+} + SO_4{}^{2-} + {}^{-}O_3SO\cdot}$$



Substitution occurs in the para position unless that is blocked, when some ortho hydroxylation (hydrolysis being assumed) occurs (21, 304). 2-Naphthol becomes substituted in the 1-position (306). However, the supposed radical-ion

$^{-}O_3SO\cdot$ does not affect benzene, toluene, naphthalene, benzoic acid, nor nitrobenzene (53), so it cannot be very active. The Elbs reagent causes exclusively ortho hydroxylation of arylamines (51, 53), just as the undoubtedly radical generator benzoyl peroxide does (127). This is additional evidence for a radical reaction but it leaves the problem of the difference in orientation between phenols and arylamines completely unsettled.

The silver-catalyzed oxidation of various aromatic compounds with persulfate often gives phenols in 1–5 per cent yield (17, 18). In acid solution *p*-cresol yields *p*-toluhydroquinone by an unusual rearrangement (273).

Monoperoxysulfuric acid oxidizes phenol to catechol and hydroquinone (26), *m*-nitrophenol to 3- and 4-nitrocatechols, and *p*-nitrophenol to 4-nitrocatechol (25).

Other inorganic peroxy acids besides those derived from sulfur can cause aromatic hydroxylation. The catalytic effects of vanadium and chromium oxides (294) and osmium tetroxide (295) have been attributed to the formation of such peroxy acids. Benzene is hydroxylated in trace amounts by peroxychromic acid, but not by peroxyboric or peroxycarbonic acid (195). The best studied case is that of peroxynitrous acid, HOONO, most readily derivable from hydrogen peroxide and nitrous acid. The radicals from peroxynitrous acid may cause hydroxylation or nitration or both (176, 196, 274). Substitution products formed (always in small yield) with peroxynitrous acid are shown in table 8. The hydroxyl group tends to enter in the ortho or para position, and the nitro group in the meta position, with respect to the original substituent. When both groups enter, they become ortho or para to each other. This is considered to favor a process whereby first a hydroxyl and then a nitro radical adds to the ring, after which the ring reverts to aromatic structure by loss of water, nitrous acid, or hydrogen. The homolytic character of the reaction is confirmed by the unusual orientation of nitro groups in the reaction of quinoline (274).

The oxidation of phenols with a mixture of 30 per cent hydrogen peroxide and

TABLE 8

Substitutions with peroxynitrous acid

Aromatic Substrate	Products[a] (Major Ones in Italics)	Reference
C_6H_6	*$C_6H_5NO_2$, o-$HOC_6H_4NO_2$*, *p*-$HOC_6H_4NO_2$, *p*-$C_6H_4(NO_2)_2$, C_6H_5OH, 2,4-$(O_2N)_2C_6H_3OH$, 2-O_2N-4-$C_6H_5C_6H_3OH$	(177)
$C_6H_5CH_3$	*$CH_3C_6H_4NO_2$* (isomers), *2-CH_3-4-$O_2NC_6H_3OH$*, 4-CH_3-2-$O_2NC_6H_3OH$	(177)
$C_6H_5NO_2$	*o- (35%), m- (12%)*, and *p*-(51%)nitrophenols; *o- (6%), m- (91%)*, and *p*-*(6%)* dinitrobenzenes, 2-O_2N-4-(*p*-$O_2NC_6H_4$)C_6H_3OH (?)	(177)
C_6H_5Cl	*o-ClC_6H_4OH, m-$ClC_6H_4NO_2$, 2-O_2N-4-ClC_6H_3OH*, *p*-$ClC_6H_4NO_2$	(177)
C_6H_5OH	*o-$C_6H_4(OH)_2$, p-$C_6H_4(OH)_2$*, *o*- and *p*-$O_2NC_6H_4OH$	(177)
$C_6H_5N(CH_3)_2$	*o*- and *p-$O_2NC_6H_4N(CH_3)_2$*	(177)
$C_6H_5OCH_3$	*o-$O_2NC_6H_4OH$, 4-CH_3O-2-$O_2NC_6H_3OH$*, 6 CH_3O-2-$O_2NC_6H_3OH$	(177)
$C_6H_5OC_2H_5$	*o-$C_2H_5OC_6H_4OH$, 6-C_2H_5O-2-$O_2NC_6H_3OH$*, 6-C_2H_5O-2,4-$(O_2N)_2C_6H_2OH$	(196)
$C_6H_5OC_3H_7$	6-C_3H_7O-2,4-$(O_2N)_2C_6H_2OH$	(196)
$C_6H_5COCH_3$	*m-$O_2NC_6H_4COCH_3$, 2-HO-3-$O_2NC_6H_3COCH_3$*, *o* $HOC_6H_4COCH_3$	(196)
Quinoline	6- and 7-$O_2NC_9H_6N$, $(O_2N)_2C_9H_5N$ (?)	(274)

(a) Percentage yields in italics refer not to the efficiency of conversion of the substrate, but to the ratio of isomers formed in a single run. The efficiency of conversion of the substrate to substituted products is usually <10 per cent.

glacial acetic acid at room temperature probably involves peroxyacetic acid. The reagent converts phenol to pyrocatechol and hydroquinone, *o*-cresol to *p*-toluhydroquinone, *m*-cresol to the same compound and orcinol, *p*-cresol to 4-methylpyrocatechol, *p-tert*-butylphenol to 3-*tert*-butyl-1,2,4,5-benzenetetrol, and either thymol or carvacrol to 3-isopropyl-6-methyl-1,2,3,5-benzenetetrol (190).

Benzothiazole heated with benzoyl peroxide yields a little 4-hydroxybenzothiazole among other products (305).

D. Electrolytic hydroxylation

Electrochemical oxidations frequently proceed by a radical mechanism. A characteristic behavior of the aromatic nucleus in such processes is hydroxylation (55, 133, 134), although subsequent conversion to quinones and further degradation products enormously complicates matters. Thus benzene yields, among other things, a little phenol, catechol, and *o*-phenoxyphenol (302), toluene gives cresols or at least their conversion products (296, 302), and benzoic acid produces 2-, 4-, 2,5-, and 3,4-hydroxylated benzoic acids (302). Benzonitrile is hydroxylated in the 2- and 5-positions, benzenesulfonic acid in the 3- and 4-positions, and naphthalene in the 1-position (55, 133, 134). However, the failure of nitrobenzene to undergo hydroxylation shows that electrolytic oxidation is not fully comparable to phenylation. At best, like other electrolytic substitutions, it is liable to give poor yields because the high concentration of radicals at the surface of the electrode favors side reactions and consecutive reactions (168).

E. Other hydroxylations

There are scattered observations on the nonpreparative but surely radical oxidation of liquid benzene to phenol by chlorine monoxide, air in the presence of water and palladium, and air in the presence of the rays from radium (43). Irradiation with radium produces *o*- and *p*-nitrophenol from nitrobenzene (250), and the related conversion to *p*-nitrophenol by exposure of nitrobenzene vapor to ultraviolet light probably involves oxygen atoms (182):

$$C_6H_5NO_2 \xrightarrow{h\nu} C_6H_5NO + O$$

$$C_6H_5NO_2 + O \longrightarrow p\text{-}HOC_6H_4NO_2$$

Little is known of the way in which aqueous potassium ferricyanide oxidizes polynitro aromatic compounds to phenols, e.g., 1,3,5-trinitrobenzene to picric acid (191). The ease of methylating such compounds with radicals and the conversion of 2-naphthol to 1-(2-naphthyloxy)-2-naphthol by the ferricyanide reagent (318) suggest that the hydroxylation also involves radicals. The same may be said of the remarkable production of nitrophenols, including *o*-nitrophenol, by the decomposition of 1′,1′,1′-trinitrobenzeneazomethane in benzene, 2-ethoxyethanol, or carbon tetrachloride (325).

Much effort has been expended upon the direct vapor-phase oxidation of benzene to phenol because of its commercial attractiveness, and some recent reviews are available (77, 112). Thermal conversion of benzene and air, with either homogeneous or heterogeneous catalysts, has been most studied. The best yield (10 per cent per pass, 77 per cent ultimate) has been achieved by passing excess benzene with oxygen, sulfur dioxide, and an inert carrier gas over a supported catalyst containing copper, silver, or gold and also a transition metal at 350–550°C. and a pressure of 100–300 lb./sq. in.; toluene thus gives chiefly *m*-cresol (331). Air and excess benzene at 370–450°C. and a pressure of 500–2000 lb./sq. in. produce up to 30 per cent of phenol per pass when aliphatic compounds are present as promoters, to supply initiating radicals (112, 223, 224a). The same kind of promoters are more or less effective also at 1 atm. (238, 249). Some kinetic studies of the reaction uncatalyzed except by reactor surfaces have been reported (237a, 239, 276a). Alternatively the oxygen may be made atomic by electric discharge; at 6–12 mm. pressure, such oxygen oxidizes benzene to phenol in about 10–12 per cent yield per pass at 100–340°C., the extent of side reactions being unknown (77). At lower conversions (<4 per cent) and higher pressure (750 mm.), air and benzene give 18–30 per cent yields of phenol and some catechol, resorcinol, and hydroquinone, but the consumption of electric power is prohibitive (376, 377, 378, 379) Under approximately similar conditions toluene gives some cresols, mostly *o*-cresol (4–7 per cent overall yield), besides products of side-chain attack (236, 380, 381). Toluene and air at 210°C. and 1500 lb./sq. in. produce a little 4-methylresorcinol (308); here, as from benzene (378), the formation of resorcinols is unexpected, since almost no other radical substitution meta to a hydroxyl group is known. More typically, the oxidation of phenol by air at 610–650°C. yields dibenzofuran and traces of 2,2′-biphenol, along with other products (237).

The greater resistance of nitrobenzene to oxidative destruction suggested its vapor-phase oxidation by air, but only a 1.5 per cent yield of *o*-nitrophenol was obtained. Probably this was the only phenol volatile enough to escape destruction on the heterogeneous catalyst (288).

The mechanism of the biological hydroxylation of aromatic nuclei is not understood, and some similarities to hydroxylation by radical attack have been pointed out (52, 339, 363). An ascorbic acid–iron complex–oxygen model system for such hydroxylation gave the products and yields shown in table 9 (56).

TABLE 9

Hydroxylated aromatic compounds produced in an ascorbic acid system (56)

Substrate	Product	Yield
		per cent
$C_6H_5NHCOCH_3$	*p*-$CH_3CONHC_6H_4OH$	17
	o-$CH_3CONHC_6H_4OH$	12
$C_6H_5NH_2$	*p*-$H_2NC_6H_4OH$	9
o-HOC_6H_4COOH	2,5-$(HO)_2C_6H_3COOH$	55
C_9H_7N	3-HOC_9H_6N	15
p-$HOC_6H_4CH_2CH_2NH_2$	3,4-$(HO)_2C_6H_3CH_2CH_2NH_2$	25

VIII. ALKOXYLATION

Direct attack of alkoxyl radicals on an aromatic nucleus is unknown. No alkoxylation is caused by tetralin hydroperoxide (338), di-*tert*-butyl peroxide (132, 322, 386), cyclohexenyl peroxide (34), and bis(triphenylmethyl) peroxide (407). Electrolytic methoxylation of benzene also fails (267).

Two instances of alkoxylation by transfer substitution have been reported, both for benzoic acid. In one case the generating radicals came from benzoyl peroxide and the alkoxyl radicals from isobutyl alcohol; *o*- and *p*-isobutoxybenzoic acids were produced (157). Some doubt of the accuracy of this observation has been expressed, since no alkoxyl radicals are formed from diacetyl peroxide and alcohols (261). Nevertheless, autoxidizing tetralin in ethanol converted benzoic acid to ethoxybenzoic acids (148).

IX. ACETOXYLATION

Acyloxylations must necessarily compete with decarboxylation:

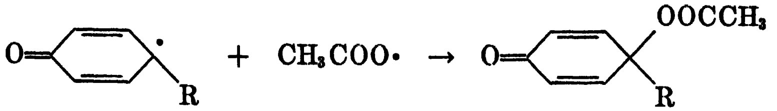
$$R\cdot + CO_2 \leftarrow RCOO\cdot \xrightarrow{ArH} RCOOAr, \text{etc.}$$

It follows that the substitution will be most successful with very reactive substrates such as polynuclear compounds and phenols. Indeed, no acetoxylation of noncondensed-ring aromatic hydrocarbons is established, although there is evidence of nuclear attack in diphenylmethane and triphenylmethane during the electrolysis of sodium acetate in acetic acid (277). Otherwise, acyloxy radicals do not affect benzene (33, 84, 141, 413), and they abstract hydrogen from any side chain present (259).

Naphthalene is substituted in the 1-position by acetoxy radicals generated either electrolytically (277) or from lead tetraacetate (136). Evidence for an ionic rather than a radical mode of decomposition of lead tetraacetate in carboxylic acids has been presented (300), but the radical mechanism of attack on aromatic substrates is still generally accepted. Anthracene with lead tetraacetate yields the 9-acetoxy derivative (292), 1,2-benzanthracene the 10-acetoxy (137), and 3,4-benzpyrene the 5-acetoxy (138, 139), but the others may resemble anthracene in going through an isolable dihydro diacetoxy adduct (140), so that calling the reaction a substitution is questionable. 10-Acetamino-3,4-benzpyrene is acetoxylated in the 5-position, 5-acetamino-3,4-benzpyrene probably in the 10-position (139), and phenanthrene (by manganese triacetate) in the 9-position (417).

The acetoxylation of some para-substituted *N*-arylacetamides by phenyl iodosoacetate appears, by its orientation and otherwise, to be ionic in character (29).

Phenols are attacked as usual by way of transfer substitution. The quinonoid forms of the radicals derived from ortho- and para-alkylated phenols tend to become stabilized as quinol derivatives by addition of acetoxy radicals (71, 394, 395, 397).



Even for structures in which tautomerization to phenols is not thus blocked, the reaction does not often stop at simple acetoxylation. Nevertheless such substitution by means of acetyl peroxide in acetic acid has been observed: *o*-cresol is acetoxylated in the 4- or 6-position, *p*-cresol in the 2- or 6-position, *m*-cresol in the 2-, 4- or 6-position, and 2,4-xylenol in the 5- (?) or 6-position (396).

At 80°C. anisole is slowly acetoxylated by lead tetraacetate in acetic acid but not by acetyl peroxide in ethyl ether–acetic acid. This has been taken to disprove the ability of acetoxy radicals to attack phenyl ethers (72), but the relatively rapid destruction of such radicals by the aliphatic ether makes any such conclusion unjustified. The reaction with lead tetraacetate doubtless involves both acetoxy and *p*-methoxyphenyl radicals, for the latter substitute in added benzene or nitrobenzene, yielding 4-methoxybiphenyl or its 4′-nitro derivative. The aryl radicals do not affect carbon tetrachloride, in which *p*-methoxyphenyl anisate is an unexpected product (72). In the absence of solvent, lead tetraacetate also causes *p*-acetoxylation of phenetole, isopropyl phenyl ether, and benzyl phenyl ether, but benzyl *p*-tolyl ether is substituted in the methyl group (31, 72). In 1-methoxynaphthalene the 4-position reacts, and in 2-methoxynaphthalene the 1-position (394).

Substitution in anisole during the electrolysis of potassium alkanoates in alkanoic acids with graphite or platinum electrodes has been observed. Mixed methoxyphenyl propionates (24 per cent yield) and valerates (13 per cent) were thus obtained, and the ortho–para ratio for acetoxylation was about 70:30 (185). The *o*-, *m*-, and *p*-methoxyanisoles also react in this way.

X. BENZOYLOXYLATION

It has been reported that benzoyloxy (benzoxy, benzoate) radicals, $C_6H_5COO\cdot$, do not substitute in benzene (179) or chlorobenzene (341) at 80°C., although they strip hydrogen therefrom. The production of mixed chlorophenyl benzoates from chlorobenzene and silver iodide dibenzoate at 130°C. (58) and from benzoyl peroxide decomposed in carbon tetrachloride (234) is apparently due to transfer substitution. Substituted phenyl benzoates are also obtained from aromatic substrates and silver bromide dibenzoate. However, the formation of mainly *m*-nitrophenyl benzoate from nitrobenzene and of *p*-chlorophenyl benzoate from chlorobenzene suggests that the substituting entity is then the benzoyloxy cation (58). Since there is evidence for the production of radicals from silver benzoates and bromine, at least in carbon tetrachloride (30, 109), the type of reaction may be mixed.

Benzoyloxylations with benzoyl peroxide occur in favorable circumstances, as shown in table 10.

A transfer-substitution course has been proposed to account for one product

TABLE 10

Benzoyloxylation of aromatic nuclei(a) *by benzoyl peroxide*

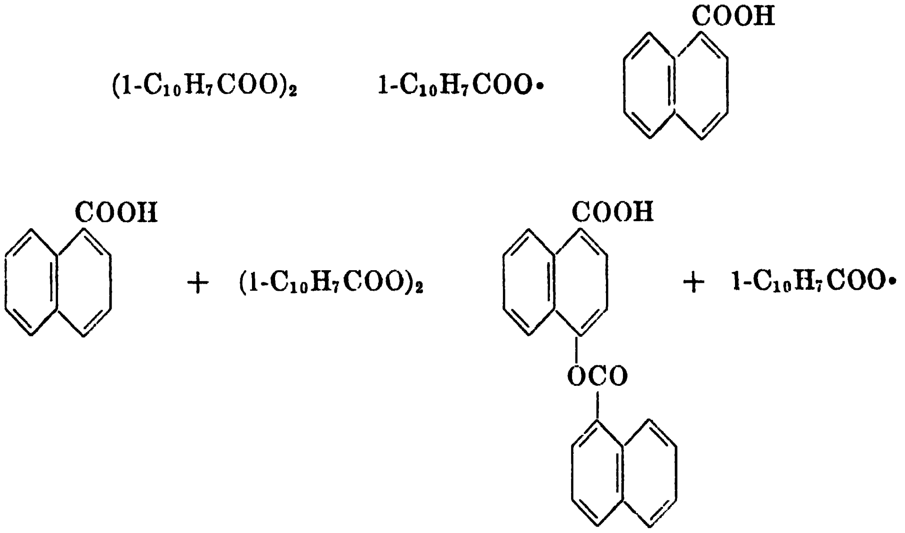
Substrate	Positions of Benzoyloxylation and Yield(b)	Reference
$1,2,3\text{-}C_6H_3(OCH_3)_3$	4 and 5 (*ca.* 20%)	(313)
$C_{10}H_8$	1 and 2	(52)
$1\text{-}ClC_{10}H_7$	2 (0.9%), 4 (16%), and 5 (14%)	(102)
$1\text{-}BrC_{10}H_7$	2 (0.7%), 4 (41%), and 5 (20%)	(102)
$1\text{-}O_2NC_{10}H_7$	2 (3%), 4 (18%), and 5 (10%)	(102)
Anthracene	9 (15%)	(341)
9-Methylanthracene	10(c)	(341)
1,2-Benzanthracene	10	(341)
3,4-Benzpyrene	5 (33%)	(341)

(a) Except phenols and amines.

(b) Based on benzoyl peroxide.

(c) Along with another benzoyloxylated product, 10-[2-(9-anthryl)ethyl]anthranol benzoate.

of the thermal decomposition of 1-naphthoyl peroxide (but not the 2-isomer) in carbon tetrachloride (256).


$(1\text{-}C_{10}H_7COO)_2$
$1\text{-}C_{10}H_7COO\cdot$
COOH
COOH
$+$ $(1\text{-}C_{10}H_7COO)_2$
COOH
$+$ $1\text{-}C_{10}H_7COO\cdot$
OCO

As with other radical sources, phenols and amines characteristically react with benzoyl peroxide by transfer substitution. Sometimes transbenzoylation modifies the original hydroxyl or amino group. Phenols (90, 91), *N*-alkylanilines (127), and the one *N*-arylaniline studied (151) yield almost entirely *o*-benzoyloxylated products unless the ortho positions are blocked, when para substitution occurs (see table 11). If the para position also is occupied, as in mesitol, no aromatic substitution products are formed (92, 395).

The mechanism for reaction of dialkylanilines is slightly different, since no

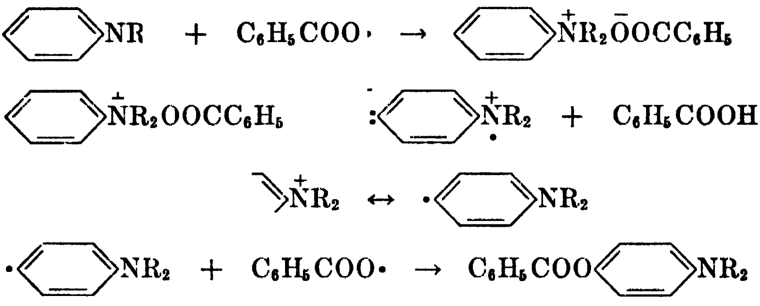
TABLE 11

Benzoyloxylation of phenols and amines with benzoyl peroxide

Substrate	Positions of Benzoyloxylation	Yields[a]	Reference	Substrate	Positions of Benzoyloxylation	Yields[a]	Reference
		per cent				*per cent*	
C_6H_5OH	2 and 4	2% total, in ratio *ca.* 4:1	(90)	$C_6H_5NHC_4H_9$-*n*	2	35	(127)
				$C_6H_5NHCH_2CH_2CH(CH_3)_2$	2	20	(127)
o-$CH_3C_6H_4OH$	6	Trace	(90)	$C_6H_5NHCH_2C_6H_5$	2	8	(127)
m-$CH_3C_6H_4OH$	6	15–20	(90)	*o*-$CH_3C_6H_4NHCH_3$	6	8	(127)
p-$CH_3C_6H_4OH$	2	30–40	(90)	*m*-$CH_3C_6H_4NHCH_3$	6	10	(127)
2,4-$(CH_3)_2C_6H_3OH$	6	30–40	(90)	*p*-$CH_3C_6H_4NHCH_3$	2	31	(127)
3,5-$(CH_3)_2C_6H_3OH$	2	15–20	(90)				
2,6-$(CH_3)_2C_6H_3OH$	4	10	(92)	*p*-$ClC_6H_4NHCH_3$	2	19	(127)
m-$CH_3OC_6H_4OH$	6	15–20	(92)	1-$C_{10}H_7NHC_2H_5$	2	40	(127)
p-$CH_3OC_6H_4OH$	2	30–40	(92)	1,2,3,4-Tetrahydroquinoline	8	16	(127)
$C_6H_5NHCH_3$	2	30	(127)	$(C_6H_5)_2NH$	2	—	(151)
$C_6H_5NHC_2H_5$	2	37	(127)	$C_6H_5N(CH_3)_2$	4	15	(218)
$C_6H_5NHCH_2CH_2CH_3$	2	20	(127)	$C_6H_5N(C_2H_5)_2$	4	15	(218)

[a] Based on benzoyl peroxide.

removal of hydrogen from nitrogen is possible. It is here represented in simplified form (218, 219, 221), involving a semiquinone stage.



Para substitution appears to be the rule (169, 218, 219, 221); this also differentiates the process from the benzoyloxylation of phenols and other anilines.

XI. HALOGENATION

Fluorine, chlorine, and bromine atoms, more than other radicals, tend to *add* to aromatic nuclei, yielding hexahalogenated cyclohexanes (and in the case of fluorine, products of polymerization and degradation). When this tendency is associated with the well-known proclivity of chlorine and bromine atoms to enter side chains, it is understandable that few clear-cut atomic halogenations of the ring are known. The one such fluorination is that of pyridine, which yields 2-fluoropyridine and thence a difluoro derivative in a liquid-phase reaction (361). Chlorine atoms from sulfuryl chloride (255) have caused no such substitution, and while *N*-halogenated imides, especially *N*-bromosuccinimide, probably yield halogen atoms, the reaction of these with aromatic nuclei is usually slow and succeeds only with the more reactive ones, such as phenolic ethers and polynuclear compounds (62, 123). Transfer substitution has been proposed as a chain sequence for such displacements (2). Evidence for both ionic and radical mechanisms of both substitution and addition of bromine in naphthalene has been adduced (286).

The production of brominated phenyl benzoates from silver benzoate and bromine has been interpreted in terms of organic and bromine radicals (189), but the earlier finding that *m*-bromobenzoic acid and *o*- and *p*-bromophenols are the ones formed (46) remains evidence for bromine cations as the active agent (*cf.* silver bromide dibenzoate, page 108). More certainly radical-produced are the chlorobenzoic acids from benzoic acid and aqueous ferric chloride complexes irradiated with ultraviolet light, but these were not further characterized (36).

Irradiation of ethyl bromide and an aromatic substrate with slow neutrons causes substitution by Br^{80} cations and Br^{82} atoms, both arising from the Szilard–Chalmers effect. In toluene, 90 per cent of the bromine goes to the side chain, but the ratio of *o*-, *m*-, and *p*-bromotoluenes (measured by oxidation and separation of the bromobenzoic acids) is about 4:1:2 (154). For other aromatic substrates the ratios are: nitrobenzene, 2.0:0.64:1; methyl benzoate, 20:2.5:1; and ethyl benzoate, 25:2.1:1 (240). From the relative rates of reaction with Br^{82} in competitive brominations, it was concluded (152, 153, 241) that the substitution involves both atoms and cations. The Br^{82} atoms are supposed to dominate the reactions with nitrobenzene and other electron-poor rings, and the Br^{82} cations those with anisole and other rings carrying electron-rich groups.

Another example of a reaction of mixed type is vapor-phase halogenation at 200–700°C. In the chlorination and bromination of monohalogenated benzenes (387, 403, 404, 405), naphthalene (362, 401), pyridine (60, 193, 194, 289, 402), quinoline (244), and thiophene (231), there is a marked dependence of isomer ratio on the temperature of reaction. At about 400°C. (250°C. for the chlorination of pyridine, 700°C. for thiophene) a gradual transition from "normal" to "statistical" orientation occurs. The former is the result of ordinary electrophilic substitution, whereas the latter represents a comparatively indiscriminate attack of radicals on all open positions, complicated somewhat by a steric effect that reduces the accessibility of the ortho positions. The work has been reviewed recently (400).

The polar reaction is favored by electropositivity of the halogen: iodine and pyridine even at 500°C. yield only 3,5-diiodopyridine and some of the pentaiodo derivative (340). It is favored also on surfaces, such as that of graphite, and by metallic halides such as ferric and cupric bromides. Light hinders it. Finally it is favored by electron availability in the aromatic nucleus: naphthalene requires a higher temperature than pyridine or the halogenobenzenes to undergo the same degree of radical halogenation, thiophene a still higher one, and phenol never does give the meta isomer in quantity.

In what appears to be a reaction of this general class, cyanogen and benzene at 740°C. produce not only benzonitrile but also isophthalonitrile and terephthalonitrile (245).

XII. OTHER SUBSTITUTIONS

The high-temperature reactions of sulfur with toluene (222) and ethylbenzene (165) yield exclusively products of side-chain substitution, as would be expected in a homolytic process. Sulfur and benzene, however, at 350°C. give small amounts of thiophenol and phenyl sulfide, and larger ones of diphenyl disulfide, thianthrene, and tars (165). No doubt the substitution would go more smoothly with naphthalene.

The dichlorophosphino radicals, $Cl_2P\cdot$, from phosphorus trichloride and benzoyl peroxide, do not attack benzene (79). A mixture of silicon tetrachloride and benzene subjected to silent electrical discharge yields some phenyltrichlorosilane, but by way of phenyl radicals rather than trichlorosilyl radicals as substituting intermediates (8). Similarly, triphenylsilyl radicals do not substitute on the ring in chlorobenzene (96).

The predominant formation of ortho-substituted derivatives by the mercuration of nitrobenzene, benzoic acid, and benzophenone (242, 399) has long been considered anomalous. To explain this orientation, it has been implied (265) that mercuration by mercuric acetate in nonpolar solvents is a radical-controlled process. The attacking species is indeed not very selective, but its nature remains uncertain (57).

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HOMOLYTIC AROMATIC ARYLATION

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I. INTRODUCTION

This article represents an attempt to assemble the relevant data, much of it recent, associated with homolytic aromatic substitution reactions and to assess the progress that has been made towards the complete understanding of this and other types of aromatic substitution. Certain assumptions are made, and undoubtedly the simplified picture presented will be modified by further experimental and theoretical work. Examination of the available data on the subject reveals a number of anomalies, and these have been included to serve as criticism of the outlined suggestions and as pointers to future lines of thought.

Ingold (195), in 1938, distinguished between two modes of bond fission:

$$\textit{Heterolysis:}\quad A{:}B \rightarrow A^- + B^+ \qquad (1)$$

$$\textit{Homolysis:}\quad A{:}B \rightarrow A\cdot + B\cdot \qquad (2)$$

where A and B are atoms or groups of atoms. The latter reaction is characterized by the production of neutral fragments, each possessing an odd unpaired electron. The term "free radical" is applied in this sense and so includes some inorganic substances, for example, nitric oxide.

Since more energy is required to separate the charged particles of equation 1 than the neutral fragments of equation 2, it would be thought that the latter reaction would be favored, and in the gas phase this is certainly true. However, for the majority of reactions in solution, particularly with solvents of high dielectric constant, fission by reaction 1 predominates because the solvation of the resulting ions results in an energetic advantage being given to this mode of fission. In solution, therefore, homolytic reaction is the exception rather than the rule.

The existence of organic radicals was experimentally demonstrated by Gomberg (132) in 1900, when working with the hexaarylethanes. The idea of an anomalous valency for carbon was not a popular one, but the accumulation of facts from many fields has resulted in the establishment of the concept. Organic free radicals have been divided into two classes: (*1*) those of long life, like the triarylmethyls, which are stabilized by resonance; (*2*) those of short life, like phenyl and methyl. It is with the reactions of radicals of the second type that this article is concerned.

The inference that short-lived radicals are unstable is erroneous; the contrary is the case. The reason why they cannot be prepared in large quantity is not that their molecules break down; indeed, a single radical completely isolated from all contact with other molecules would doubtless remain unchanged indefinitely.

The reason is instead that these substances are so extraordinarily reactive that each entity undergoes some sort of chemical change, in an attempt to satisfy its normal valency requirements, before it has made a large number of collisions with other molecules. Strictly speaking, therefore, the term "short-lived," when applied in description of a free radical, means nothing unless the environmental conditions are also stated. It is very difficult to demonstrate physically the existence of these radicals in solution, as the techniques usually applied to the detection of radicals of the triarylalkyl type, e.g., color reactions and magnetic measurements, completely fail. The presence of radicals of short life is inferred from their reactions, on account of both the complex kinetics which they exhibit and the natures of the chemical products that are obtained.

Free radicals react in three main ways:

By dimerization, or combination of the radicals:

$$R\cdot + R\cdot \rightarrow RR \tag{3}$$

By disproportionation, involving mutual hydrogenation and dehydrogenation:

$$2RCH_2CH_2\cdot \rightarrow RCH_2CH_3 + RCH{=}CH_2 \tag{4}$$

By radical transfer, which is expressed by the general equation:

$$R\cdot + XR' \rightarrow RX + R'\cdot \tag{5}$$

In the last reaction the nature of the final products is also dependent on the radical $R'\cdot$. It may react as in equation 5 to give another radical $R''\cdot$, which may or may not be the same as $R'\cdot$. If it is the same, then a chain reaction has been set up and the process repeats itself until the chain is somehow interrupted. If the radical $R'\cdot$, or $R''\cdot$, is relatively unreactive, then the transference (reaction 5) has resulted effectively in the termination of the reaction.

In many instances these reactions may occur simultaneously, and the total reaction may appear very complex. In defined cases, however, certain of these reactions are favored relative to the others, and specific compounds preponderate in the product. This is illustrated by a comparison of the reaction medium of the gas phase with that of the liquid phase for, though the reactions may be initiated in the same way in both media, there are great differences in the types of reaction occurring. For example, in the photolysis of ketones and the pyrolysis of certain organometallic compounds, in the gas phase, where collisions between radicals can readily occur, reactions 3 and 4 predominate, whilst in solution, where the radicals are surrounded by solvent molecules, reactions between radicals are unlikely unless the life of a radical is for some reason prolonged. With labile radicals in solution the radical–solvent interaction (equation 5) is the most important reaction, and it is clear from this equation that the product is determined by both the radical and the solvent.

With aromatic solvents, alkyl radicals behave differently from aryl radicals. Thus alkyl radicals, in general, react with aromatic solvents by reactions other than that of direct substitution. They do, however, effect substitution in some cases, and this will be discussed at a later stage. Similar considerations are valid in the comparison between the reactions of a given radical with either aliphatic or aromatic solvents, only the latter being susceptible to homolytic substitution.

During the last few years these homolytic aromatic substitution reactions have been studied in considerable detail, and the results have been periodically discussed. However, the data have not yet been assembled in a comprehensive review and the practical results have not been investigated as to their reliability and significance.

Dermer and Edmison (92), in their review article, have summarized the extensive practical work carried out over the whole subject field. The present review is concerned with a more limited field: namely, with the more recent quantitative work carried out with aromatic solvents and, unless specifically mentioned, aryl radicals, particularly phenyl. The article consists of two parts: firstly, a critical discussion of the appropriate practical work, leading to presentation of the relative rates for homolytic reaction and the corresponding partial rate factors; and secondly, an examination of the theoretical treatments for aromatic substitution. The application of the theoretical treatments to the case of homolytic reactions is considered, and the quantitative predictions suggested by calculations based on mathematical results already available from these methods are compared with the new experimental data.

II. Heterolytic and Homolytic Aromatic Substitution

Although the reactions of organic compounds are reactions of nonionic substances when compared with those of inorganic compounds, it is accepted that the course of the majority of organic reactions is determined by the charge distribution within the molecule. Thus, owing to the fact that homolytic reaction is less frequently encountered, the so-called "normal laws" of aromatic substitution, developed as the result of experiment, are laws governing the *heterolytic* reactions in which the organic substances take part.

Heterolytic reagents are of two kinds: those which seek out the centers of high electron density, i.e., electrophilic reagents, and those which react at electron-deficient positions, i.e., nucleophilic reagents. Hence, in the majority of aromatic substitution reactions, such as nitration, halogenation, sulfonation, and diazo-coupling, a proton is replaced by an electrophilic reagent capable of accommodating a pair of electrons, e.g., the nitronium ion, NO_2^+, which is responsible for most aromatic nitrations. Many nucleophilic reactions of aromatic substitution are also known, and these have been reviewed recently by Bunnett and Zahler (43).

The history of the development of the theories of heterolytic aromatic substitution is long and outside the scope of this review (8, 246).

The more recent work of the so-called English School has resulted in the establishment of what may be called the "normal laws" of aromatic substitution. These are based mainly on studies of nitration (14, 15, 21, 185, 194, 197, 198, 247), i.e., a reaction of electrophilic substitution. On theoretical and experimental grounds a directing group (X), attached to the aromatic nucleus (C_6H_5) in the compound C_6H_5X, may be placed in one of two main categories. Thus, for this type of substitution [the rules are reversed for nucleophilic reactions (8, 19, 42, 43, 113, 246)], the following X substituents are ortho–para directing and activate the nucleus for reaction relative to benzene:

$$NH_2 > OH > OCH_3 > OCOCH_3 > CH_3 > Cl; Br > C_6H_5 > CH_2COOH \quad (6)$$

whereas the following groups are meta directing and deactivating:

$$\overset{+}{N}(CH_3)_3 > NO_2 > SO_3H > CHO > COCH_3 > COOH > \overset{+}{N}H_3 \quad (7)$$

The situation is a little more complex in that certain anomalies, which are accommodated by the general theory, occur. Thus, for example, the halogens are deactivating groups but are ortho–para directing.

The work of Ingold and coworkers in this field is well known (21, 194, 197, 198) and was important in providing quantitative data to describe the phenomena. The work resolved itself into two parts: (*1*) the determination of the quantities ${}^{X}_{H}K$, i.e., the ratio of the total rate of nitration of the monosubstituted benzene derivative, C_6H_5X, relative to that of benzene, C_6H_6; (*2*) the estimation of the proportions in which the three isomers r-$NO_2C_6H_4X$ (r = o-, m- or p-), were formed in the nitration of C_6H_5X alone.

The combined results of these experiments allowed the evaluation of the partial rate factors ${}^{X}_{H}k_r$. Each of these factors expresses the change in the specific rate of substitution at any position r in the nucleus due to the presence of the group X, i.e., it is the *ratio* of the rate of reaction at the point r in the molecule C_6H_5X relative to that at any one position in benzene. It must be remembered that the quantities ${}^{X}_{H}K$ and ${}^{X}_{H}k_r$ are pure numbers; they have no dimension in time. Table 1 presents some of the values obtained.

For toluene the figures are greater than unity and show that the methyl group activates all the positions r, i.e., toluene is more readily nitrated than benzene. Moreover, the order of the ${}^{X}_{H}k_r$ values, i.e., $p > o > m$, necessarily implies that this is the sequence of reactivities of the nuclear positions. The carbethoxy group, $COOC_2H_5$, shows general deactivation, with the meta position least affected, and the halogens show themselves to be exceptions to the rules, as mentioned above. Details concerning other groups, e.g., *tert*-butyl,

TABLE 1

Partial rate factors for nitration (291°K.)

	${}^{X}_{H}k_o$	${}^{X}_{H}k_m$	${}^{X}_{H}k_p$	${}^{X}_{H}K$	References
$-CH_3$	40.0	3.0	51.0	23.0	(197)
$-COOC_2H_5$	0.0026	0.0079	0.001	0.0037	(198)
—F	—	—	—	0.15	(21)
—Cl	0.030	0.000	0.139	0.033	(21, 246, 247)
Br	0.037	0.000	0.106	0.030	(21, 246, 247)
—I	—	—	—	0.18	(21)
—OH[a]	—	—	—	$\sim 10^4$	
$-NO_2$[a]	0.24×10^{-6}	2.75×10^{-6}	0.03×10^{-6}	$\sim 10^{-6}$	(185, 246)

[a] Approximate figures only.

are available (32, 60, 182). Data for halogenation (16, 17, 18, 28, 29, 61, 62, 90, 91, 223–228, 243) and sulfonation (107, 269, 278, 279) have been reported recently; e.g., for chlorination at ca. 25°C. the total relative rate values for all groups X fall into sequence (226) between the extreme figures of ${}^{N(CH_3)_2}_{H}k \sim 10^{18}$ and ${}^{NO_2}_{H}k \sim 10^{-6}$; and the partial rate factors for toluene (61, 62, 227) are ${}^{CH_3}_{H}k_o = 600$, ${}^{CH_3}_{H}k_m = 5$, and ${}^{CH_3}_{H}k_p = 870$. The differences between these figures and those of table 1 show the electron demands of the reagents to be different (29, 228) and illustrate that any set of partial rate factors applies only to the reaction for which they were determined.

Although these laws were not so clearly defined at the time, it was the separation of the apparently anomalous substitution products arising from certain reactions that first indicated the possibility of another, i.e., nonionic, type of substitution. These reactions were those whereby the preparation of biaryls was accomplished, and it was suggested (141, 159, 174) by Hey and Waters, in 1934 and 1937, that in these reactions homolytic processes were occurring. In essence, the existence of short-lived free radicals of the type of phenyl was postulated, and these entities, being electrically neutral and therefore not subject to the same electrical effects as the heterolytic reagents, effected substitution in the aromatic molecule C_6H_5X without conforming to the normal laws of aromatic substitution. These reactions can be expressed by the general equation:

$$\mathrm{Ar'M + ArH \rightarrow Ar'Ar + N\ (products)} \qquad (8)$$

where the radical Ar′•, produced from the compound Ar′M, in reaction with the aromatic solvent ArH forms the biaryl ArAr′ and ejects a hydrogen atom which is incorporated in the product N. It was later found that in homolytic substitution in ArX the general tendency was for all groups X, whatever their directing effect in heterolytic substitution, to favor predominantly reaction at the para position. The meta position was thought to be least favored and the corresponding *m*-biaryl was rarely isolated. More recent work has, however, necessitated considerable revision of these ideas.

A number of different aspects of the problem therefore present themselves for review. The reactions of equation 8 must be defined and their homolytic character clearly established; the mechanism by which the substitution is effected has to be formulated; the reasons have to be ascertained for the erroneous conclusions, mentioned above, of almost invariable para homolytic reaction; the theoretical aspects of substitution have to be considered; and finally, the new concepts of free-radical reaction have to be related to theory and practice.

III. HOMOLYTIC ARYLATION REACTIONS

Several main types of homolytic reaction, featuring interaction between aryl radicals and aromatic solvents and generally expressed by equation 8 above, may be considered. These and other reactions are reviewed by Dermer and Edmison (92). The reactions considered here are those which have been subjected to quantitative study. The biaryl ArAr′ produced usually consists of a mixture of substituted biphenyls, and in the discussion which follows this mixture will be termed the "biphenyl fraction".

A. DIAZO COMPOUNDS

1. *Diazonium chlorides etc., D reaction*

These reactions, designated by the letter D, are carried out by adding the solid diazonium chloride, or a similar compound, which is usually impure, to the organic solvent and heating the mixture. The primary reaction (241, 242, 282, 284) is the first-order decomposition of the wholly covalent molecule, producing Cl• and $C_6H_5\cdot$ radicals and liberating nitrogen:

$$C_6H_5N_2Cl \rightarrow C_6H_5\cdot + Cl\cdot + N_2 \qquad (9)$$

The addition of some metals to the reaction mixture has been shown (284) to result in the formation of metallic chlorides or organometallic compounds, even in slightly alkaline media, and this demonstrates the existence of the highly reactive radicals. Clearly, the reactions of diazo compounds (267), 1-aryl-3,3-dialkyltriazenes (111), arylazotriarylmethanes (159, 181, 293–297), and stabilized diazonium compounds (181) are analogous.

2. *Diazonium hydroxides and acylarylnitrosamines*

(a) Gomberg reaction, G reaction

The decomposition of diazohydroxides (7) in aqueous/aromatic systems was developed by Gomberg (133, 134) from the work of Bamberger (9, 10) and Kuhling (207–209). In aqueous solution at temperatures of 0–5°C. the diazotized amine is converted to a covalent diazohydroxide, and in the presence of a liquid aromatic compound the following reaction ensues:

$$Ar'N_2Cl + NaOH + ArH \rightarrow ArAr' + N_2 + NaCl + H_2O \qquad (10)$$

The reaction is essentially heterogeneous, and success depends on the ability of the aromatic compound to extract the reactive covalent hydroxide from the aqueous phase as soon as it is formed by the hydrolysis (110, 142). This is neatly demonstrated (142) by the fact that benzoic and anthranilic acids do not take part in the Gomberg reaction unless first esterified, i.e., converted from easily ionized molecules, preferring aqueous solution, to typical organic esters.

The reaction has been extended (142) to the employment of a solid aromatic compound ArH by using an organic solvent (chloroform, carbon tetrachloride) which is relatively inert towards the radicals involved and which in reaction forms compounds easily isolated from the desired substitution product ArAr′.

The products of reaction are usually very tarry and the yields of biaryl are low, ca. 10–20 per cent of the amine, with the formation of large quantities of intractable tar.

(b) Hey reaction, H reaction

The decomposition of acylarylnitrosamines, a reaction largely developed by Hey (141), is closely related to the above Gomberg reaction. Not only does this reaction yield the same products in reactions with the same aromatic solvent as the Gomberg reaction, but it also appears to react by a similar mechanism. This is not surprising in view of the fact that the acylarylnitrosamines rearrange, giving diazo-esters:

$$Ar'N(NO)COCH_3 \rightarrow Ar'N{=}NOCOCH_3 \tag{11}$$

The reaction is accomplished by adding the (usually impure) nitroso compound to the aromatic solvent at moderate temperatures. It is, therefore, a homogeneous reaction, unlike the G reaction, and has lent itself to investigation of the reaction kinetics. Thus, it has been shown (47, 141, 171, 172, 187–191, 288) that the rate-determining step is the intramolecular rearrangement (equation 11). In a non-ionizing solvent homolysis then occurs rapidly and reaction (93, 153) with the solvent gives the products indicated by equations 12a and 12b:

$$\begin{tikzcd}
 & Ar'H + N_2 + CH_3COOAr \\
Ar'N{=}NOCOCH_3 + ArH \arrow[ur, "(a)"] \arrow[dr, "(b)"'] & \\
 & Ar'Ar + N_2 + CH_3COOH
\end{tikzcd} \tag{12}$$

This dual behavior, with the Ar'• radical either abstracting a hydrogen atom or combining with the nucleus to form a biaryl, is now well established. It will be met again, and much controversy has centered around it (Section V,C).

Investigation of the reaction in a wide variety of solvents has shown that the solvent has little effect upon the decomposition kinetics (141, 171, 172) and indicates that it is unlikely that the biaryl is produced by a chain reaction involving solvent radicals Ar• and the diazoacetate (see Section III,B,2).

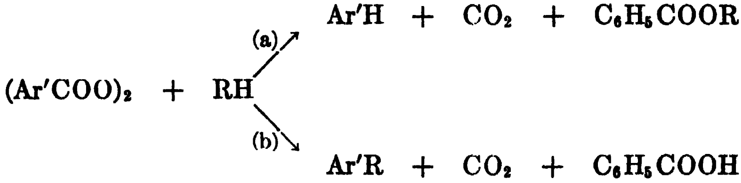
It was indicated in Section I that a free radical may react in any one of a number of different ways and that though a given mode may predominate, it does not do so exclusive of all others. It appears that the energy relationships are so balanced that many possible reactions have a definite and observable probability dependent upon the properties of the radical and the solvent. Huisgen (190) has shown that for equation 12, where $Ar'\cdot = C_6H_5\cdot$ and ArH = pyridine, the ratio of reactions (a):(b) $\sim$ 1:120, i.e., the aryl radical Ar'•, from the diazo compound, prefers nuclear substitution of ArH to hydrogen abstraction. It is conceivable that this relationship could be changed by suitable choice of ArH, e.g., if the Ar'• radical removed a hydrogen atom from the solvent to leave a radical Ar• heavily stabilized by resonance. When an aliphatic solvent is used, reaction 12a is the predominant reaction (283).

B. DIACYL PEROXIDES, P REACTION

1. Use in preparation reactions

This is undoubtedly the "cleanest" of the reactions considered. The purified peroxide, often crystalline, is added to the aromatic solvent and the decomposition is effected by heating, usually to ca. 70–80°C. Smaller quantities of tars are obtained in the product and the reported yields are higher than with the D, G, and H reactions.

Gelissen and Hermans (23, 122–129) showed that the decomposition of diacyl peroxides in various solvents (RH) obeyed their "RH scheme" (*cf.* equation 12 above), though the mechanism was not clearly defined.



$$(Ar'COO)_2 + RH \begin{cases} \xrightarrow{(a)} Ar'H + CO_2 + C_6H_5COOR \\ \xrightarrow{(b)} Ar'R + CO_2 + C_6H_5COOH \end{cases} \tag{13}$$

The accumulated evidence of this and later work (5, 23, 93, 296, 298) shows that the decomposition of any peroxide $(Ar'COO)_2$ in an aromatic solvent ArH gives rise only to the formation of compounds of the type ArAr'; e.g., the decomposition in benzene of a symmetrical disubstituted peroxide yields only the monosubstituted biphenyl. Similarly, the decomposition of benzoyl peroxide in a solvent other than benzene yields a biaryl with substituents in only one nucleus. Two conclusions follow: (*1*) the radicals from the peroxides (Ar'•, Ar'COO•) do not recombine, and (*2*) the abstraction of hydrogen atoms from the solvent by either Ar'• or Ar'COO• is not the predominant reaction, since the radical Ar• so formed would yield the symmetrical biaryl ArAr by dimerization or solvent reaction (equations 12b and 13b). The main reaction with the aromatic solvent is therefore

$$Ar'\bullet + ArH \rightarrow ArAr' + H\bullet \tag{14}$$

2. Kinetics of the decomposition of diaroyl peroxides

Much recent work has been concerned with a study of the kinetics of the decomposition of benzoyl peroxide. Several mechanisms have been proposed for this reaction, but some of these have not taken due account of the nature of the products formed in the different cases and have tended towards overgeneralization.

Brown (30), in 1940, showed by measurement of carbon dioxide evolution that the peroxide decomposition could be expressed by parallel first- and second-order reactions; i.e., if C represents the concentration of benzoyl peroxide, k'_{I} and k'_{II} are constants, and t is time:

$$\frac{-dC}{dt} = k'_{I}C + k'_{II}C^2 \tag{15}$$

The approximate first-order kinetics was confirmed by some workers (11, 78), but Nozaki and Bartlett (235, 236), in investigating a whole range of solvents, showed that in addition to unimolecular dissociation of the peroxide, now known (13, 94, 147, 148) to form two $C_6H_5COO\bullet$ radicals, there was also a chain decomposition induced by the radicals derived from either the peroxide P or the solvent SH. The chain termination was thought to be by the recombination of two radicals:

Scheme I

$$\begin{aligned}&\text{(a) } P \rightarrow 2R'\cdot\\ &\text{(b) } R'\cdot + P \rightarrow N \text{ (products)} + R'\cdot \qquad (16)\\ &\text{(c) } R'\cdot + R'\cdot \rightarrow R_2'\end{aligned}$$

where $R'\cdot$ = radical from either peroxide or solvent, i.e., $C_6H_5\cdot$, $C_6H_5COO\cdot$, or $S\cdot$. Induced decomposition by $S\cdot$ in stage (b) leads to the kinetic equation:

$$\frac{-dC}{dt} = k_i'C + k_{ii}'C^{3/2} \qquad (17)$$

Nozaki and Bartlett indicated that the induced decomposition, contributing the term $k_{ii}'C^{3/2}$ to the rate equation 17, was the main cause of variation in the observed rate of decomposition from one solvent to another, and that these rates were in the order:

Aromatic solvents[2] < ethers < alcohols < phenols < amines (18)

Some workers (53) believed that the similarity of the $S\cdot$ ($Ar\cdot$) radicals, produced from a series of aromatic solvents, was the reason for the consistently small contribution that they made to the induced decomposition. Only in one instance (150) does it appear that the nature of the products from these aromatic systems has been considered and due reservation expressed concerning the solvent-radical mechanism. The significance of the solvent radicals (12, 22, 58, 210, 252) for the case of phenol is exceptional and is discussed at a later stage.[3] In an attempt to explain the kinetic behavior of the aromatic solvents, Nozaki and Bartlett (235, 236) intimated that if the disappearance of the chain carriers (equation 16, $R'\cdot = R\cdot = C_6H_5\cdot$ or $C_6H_5COO\cdot$) was not due to the recombination of radicals (equation 16c) but resulted from reaction with the solvent to give an *unreactive* radical ($S\cdot = Ar\cdot$):

$$R\cdot + ArH \rightarrow RH + Ar\cdot \text{ (unreactive)} \qquad (19)$$

then the kinetics could be described by the equation obtained earlier by Brown (equation 15). In this event it is difficult to see how an unsymmetical biaryl is formed at all (equation 16b precluded). In addition, the stability of $Ar\cdot$ would not only tend to increase the probability of reactions of the type shown in equation 16c, but in so doing would result in the formation of the symmetrical biaryl ArAr (*cf.* Sections I and III,B,1, above).

A further scheme which has been postulated is that involving solvent radicals which are considered to yield biaryl by attacking the peroxide (equation 20b).

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[2] Exclusive of phenols and amines; e.g., hydrocarbons, nitro compounds, and chloro compounds.

[3] See references 300 and 301.

Scheme II

$$\begin{array}{lll} & \text{(a)} & P \rightarrow 2R\cdot \\ & \text{(b)} & R\cdot + P \rightarrow N + R\cdot \\ & \text{(c)} & R\cdot + ArH \rightarrow RH + Ar\cdot \\ & \text{(d)} & Ar\cdot + P \rightarrow ArR + R\cdot \\ \text{and/or} & \text{(e)} & Ar\cdot + R\cdot \rightarrow ArR \\ \text{and/or} & \text{(f)} & Ar\cdot + Ar\cdot \rightarrow Ar_2 \end{array} \qquad (20)$$

where $R\cdot = C_6H_5\cdot, C_6H_5COO\cdot$.

This mechanism was also suggested independently (96) in an attempt to explain the products of the reaction even after the kinetic work had been reported. Scheme II, however, cannot explain, either singly or together, why these solvents show no induced rate, although this is necessitated by equation 20, for Ar• will be similar to R• and must react in a similar fashion (equation 20b), and also why no dimerization products like ArAr (equation 20f) are found.

It is now possible to clarify the situation, at least for the typically aromatic solvents, for a different explanation consistent with both the kinetics and the type of product obtained may be offered. The relevant experimental data are summarized in the following conclusions: (*1*) The dimerization reaction (equation 16c) has been shown absent (see III,B,1, above), and so chain termination must involve the solvent in a reaction of the type shown in equation 19. (*2*) In order to explain the low induced rate observed for these solvents an inactive radical Ar• was postulated in equation 19. This is difficult to reconcile with the facts that (*a*) Ar• must be similar to R• (= $C_6H_5\cdot$, $C_6H_5COO\cdot$) and so must take part in the reaction, and (b) the symmetrical biaryl ArAr is not formed. (*3*) Evidence summarized in the preceding section (III,A,2; III,B,1), showing that hydrogen-atom abstraction was the minor reaction, must be considered.

Thus the chain-termination step, that is, the interaction between the radical R• and the solvent ArH, produces not an inactive solvent radical but the very highly reactive hydrogen atom. This hydrogen atom reacts immediately either with another radical R• or with the solvent and becomes effectively lost. i.e.:

Scheme III

$$\begin{array}{ll} \text{(a)} & P \rightarrow 2R\cdot \\ \text{(b)} & R\cdot + P \rightarrow N + R\cdot \\ \text{(c)} & R\cdot + ArH \rightarrow ArR + H\cdot \\ \text{(d)} & H\cdot + R\cdot \rightarrow RH \\ \text{(e)} & H\cdot + ArH \rightarrow \text{reduced compounds} \end{array} \qquad (21)$$

where R• = radical from peroxide, i.e., $C_6H_5\cdot$ or $C_6H_5COO\cdot$. Hydrogen-atom removal by reaction 21d leads to:

$$\frac{\mathrm{d}C}{\mathrm{d}t} = k_iC + k_{ii}C^{3/2} \tag{22}$$

and hydrogen-atom removal by reaction 21e leads to:

$$\frac{-\mathrm{d}C}{\mathrm{d}t} = k_iC + k_{ii}C^2 \tag{23}$$

The most important feature of scheme III is that solvent radicals play no part in the chain decomposition, and it is a necessary corollary of such a scheme that these radicals are formed only in negligible amount. It is seen that the hydrogen atom may be removed by one of the two processes, either by R• or by the solvent, and that for each separate case the overall kinetic equation is different. Qualitative reasoning indicates that the former is more probable (192, 288) for in the solvent cage, containing ($2C_6H_5COO\cdot$, ArH), when substitution is effected by a $C_6H_5\cdot$ radical, formed by decarboxylation of one $C_6H_5COO\cdot$ radical, the hydrogen atom liberated is able to unite with the remaining $C_6H_5COO\cdot$ radical to form benzoic acid. Experimentally, in the majority of peroxide reactions, the quantity of benzoic acid produced does account for about half of the peroxide. Such pseudo-termolecular collisions are quite feasible in the liquid-phase system under discussion. This suggestion accounts for the difficulty of isolating reduced material from these reactions (192). If, however, an acceptor radical, $R\cdot = C_6H_5COO\cdot$, is not available to absorb the hydrogen atom, then this may be accommodated by a solvent molecule (5). The kinetics will tend towards equation 23 and reduced compounds will appear in the reaction product.

When phenols[4] (12, 235, 236) and possibly amines (120, 121, 183, 238) (*cf.* equation 18) are used as solvents, hydrogen abstraction from the OH and NH_2 groups can take place and the high rate of induced decomposition, brought about by the important solvent radicals, leads to scheme IV, which is essentially that of equation 16:

Scheme IV

$$\begin{aligned}
&\text{(a)}\quad \mathrm{P} \rightarrow 2\mathrm{R}\cdot\\
&\text{(b)}\quad \left\{\begin{matrix}-\mathrm{R}\cdot\\ \end{matrix}\right. + \mathrm{P} \rightarrow \mathrm{N} + \mathrm{R}\cdot\\
&\text{(c)}\quad \mathrm{R}\cdot + \mathrm{SH} \rightarrow \mathrm{S}\cdot + \mathrm{RH}
\end{aligned} \tag{24}$$

where R• = radical from peroxide, i.e., $C_6H_5\cdot$ or $C_6H_5COO\cdot$.

Strong chain decomposition occurs (reactions 24b and 24c), and if this is sufficiently important all the peroxide P is consumed in the form of $R\cdot = C_6H_5COO\cdot$, the benzoyloxy radicals being unable to lose carbon dioxide because of the high rate of their reaction with the solvent. This leads to the kinetic equation:

---

[4] See references 300 and 301.

$$\frac{-\mathrm{d}C}{\mathrm{d}t} = k_{\mathrm{i}}''C + k_{\mathrm{ii}}''C^{3/2} \tag{25}$$

This observation is relevant to later discussion.

The foregoing argument demonstrates the dangers of overgeneralization and the importance of considering both the kinetics and the products together in presenting a reaction mechanism. The importance of both solvent and radical is emphasized (see Section I). Here, for a given radical, the change in solvent from a nonphenolic aromatic compound to phenol has produced a change in the nature of the decomposition.

C. LEAD TETRABENZOATE AND PHENYL IODOSOBENZOATE

Recent work (169, 170) has shown that these compounds decompose in a manner analogous to benzoyl peroxide, yielding benzoyloxy and phenyl radicals (equations 25a and 25b).

$$\left.\begin{aligned} &\mathrm{Pb(OCOC_6H_5)_4} \rightarrow \mathrm{Pb(OCOC_6H_5)_2} + 2\mathrm{C_6H_5COO\cdot} \\ &\mathrm{C_6H_5COO\cdot} \rightarrow \mathrm{C_6H_5\cdot} + \mathrm{CO_2} \end{aligned}\right\} \tag{25a}$$

$$\left.\begin{aligned} &\mathrm{C_6H_5I(OCOC_6H_5)_2} \rightarrow \mathrm{C_6H_5I} + 2\mathrm{C_6H_5COO\cdot} \\ &\mathrm{C_6H_5COO\cdot} \rightarrow \mathrm{C_6H_5\cdot} + \mathrm{CO_2} \end{aligned}\right\} \tag{25b}$$

The phenyl radicals are capable of effecting the phenylation of the aromatic compound in whose solution the decomposition is carried out, and the phenylation reaction has been subjected to quantitative study.

D. HOMOLYTIC NATURE OF THE REACTIONS

The inclusion of free-radical intermediates in some of the above reactions has been questioned by Hodgson (180), who proposed that they were not present in reactions in aqueous media, i.e., the G reaction, and that the substitutions effected by them could be explained on an ionic basis. Some of these criticisms have been answered by Hey and Waters (175). It is now certainly true that, dependent on conditions, both ionic and radical mechanisms can take place in some cases (95, 96, 154, 155, 160, 161, 163, 165, 255), e.g., the Pschorr reaction, but the following considerations show that all the reactions discussed above are essentially homolytic in character.

(i) In Section III,A,2 it was shown that, in the G reaction, benzoic acid does not undergo substitution unless it is first esterified, i.e., the reaction takes place in the nonaqueous phase, where covalent molecules may be expected to decompose to yield free radicals.

(ii) Similar chemical products are derived from all the above cases, i.e., G, H, and P reactions. The H and P reactions are known to be homolytic, as indicated by their kinetics, the insensitivity of the reaction rate to the polarity of the solvent (33), the absence of any correspondence between decomposition rate and acid dissociation constant, etc. In this context it may be noted that the phrase "similar products" does not bear close scrutiny if applied to work done before 1951 (table 3). The more recent work, however, justifies its use.

(iii) Arising from the more recent investigations, mentioned under paragraph (ii) above, it has been shown (5, 97, 161, 164, 170) that a given aromatic compound, ArX, gives identical proportions of the three isomers, r-$C_6H_5C_6H_4X$, when it reacts with radicals derived from any of the four main sources. Thus, since the H and P reactions are homolytic, the G reactions must also be so. These isomer percentages are given in table 2.

The values (table 2) indicate that for all these reactions it is the aryl radical itself, usually C_6H_5, and no other entity, such as $ArN_2\bullet$ or $Ar'COO\bullet$ for the G and P reactions, respectively, which effects the substitution, for this is the only intermediate which is common to all the reactions employed.

For the restricted field of discussion (aryl radicals with aromatic solvents) the evidence is in favor of homolytic reaction in all the D, G, H, and P reactions. The substitution is effected by the aryl radical with expulsion of a hydrogen atom (equation 14).

Returning to the historical development of free-radical substitution, it was stated above (Section II) that Hey and Waters (140, 159, 174) in 1934-37 had indicated that the apparently anomalous products isolated from these reactions could be explained by the existence of free radicals of the type of free phenyl. Before 1951, many reactions of this kind were carried out and it was believed that the general tendency was for the group X, whatever its directing effect in heterolytic substitution, to direct a homolytic reagent primarily to the para position. The meta position was least favored and the corresponding product rarely observed. These conclusions were based on a considerable volume of experimental evidence, which is summarized in table 3. They are, however, now known to be largely incorrect. This situation has arisen (286) as a result of several factors:

(i) It should be appreciated that many free-radical processes go to make up the overall homolytic reaction (Sections I and II). Since each inde-

TABLE 2*

Ratios of isomers for arylation with various radical sources (cf. table 15)

Solvent ArX	Radical Source	Reaction	Isomer Percentages			References
			Ortho	Meta	Para	
C_6H_5Cl	$C_6H_5NH_2$, $(C_6H_5COO)_2$	G, P†	62.2 ± 2	24.0 ± 2	13.8 ± 2	(5, 161)
$C_6H_5NO_2$	$C_6H_5NH_2$, $(C_6H_5COO)_2$	G, P†	58 ± 4	10 ± 2	32 ± 4	(161, 164)
	$C_6H_5NH_2$, $(C_6H_5COO)_2$	G, H, P†	60–70	0–10	30–40	(97)
	p-$BrC_6H_4NH_2$, $(p$-$BrC_6H_4COO)_2$	D, G, H, P		12.1		(164)
	p-$CH_3C_6H_4NH_2$, $(p$-$CH_3C_6H_4COO)_2$	D, G, H, P		8.6		(164)

* See Section VI,B for relevant discussion.

† Spectroscopic values.

TABLE 3

Isomers obtained in preparative arylation reactions

Reagent (Ar′• Producer)	Solvent ArX	Substitution	Reaction	References
$C_6H_5NH_2$	$C_6H_5NO_2$	p	G	(133)
$C_6H_5NH_2$	$C_6H_5NO_2$	p	D	(181)
$C_6H_5NH_2$	$C_6H_5NO_2$	$p > o$	G, H	(141)
$C_6H_5NH_2$	$C_6H_5NO_2$	p, o	D	(111)
$4\text{-}CH_3C_6H_4NH_2$	$C_6H_5NO_2$	p, o	G	(140)
$r\text{-}O_2NC_6H_4NH_2$	$C_6H_5NO_2$	p	G	(181)
$3\text{-}BrC_6H_4NH_2$	$C_6H_5NO_2$	p	G	(52)
$4\text{-}NH_2C_6H_4C_6H_5$	$C_6H_5NO_2$	$p < o$	H	(116)
β-Naphthylamine	$C_6H_5NO_2$	$p > o$ and $p < o$	G, H	(110, 162)
$(C_6H_5COO)_2$	$C_6H_5NO_2$	$p > o$	P	(159)
$C_6H_5NH_2$	C_6H_5Cl	Mixture	G, H	(141)
$C_6H_5NH_2$	C_6H_5Br	p, o	G	(133)
Methyl 4-aminophthalate	C_6H_5Cl	p, o	G	(46)
$(C_6H_5COO)_2$	C_6H_5Cl	p	P	(159)
$4\text{-}CH_3OOCC_6H_4NH_2$	C_6H_5Cl, C_6H_5Br	p, o	G	(157)
$4\text{-}CH_3C_6H_4NH_2$	C_6H_5Cl, C_6H_5Br	p, o	G	(116, 134)
Methyl anthranilate	C_6H_5Cl, C_6H_5Br	p, o	G	(157)
$4\text{-}NH_2C_6H_4C_6H_5$	C_6H_5Cl, C_6H_5Br	$p > o > m$	H	(116)
$C_6H_5NH_2$	$C_6H_5CH_3$	o, p	D	(233)
$C_6H_5NH_2$	$C_6H_5CH_3$	o, p	D	(296)
$C_6H_5NH_2$	$C_6H_5CH_3$	$o > p$	G, H	(9, 10, 133, 140)
$4\text{-}O_2NC_6H_4NH_2$	$C_6H_5CH_3$	$o > p$	G, H, D	(9, 10, 117, 202, 207–209)
$4\text{-}ClC_6H_4NH_2$	$C_6H_5CH_3$	$o > p$	G	(157)
$2\ BrC_6H_4NH_2$	$C_6H_5CH_3$	$o > p$	G	(116)
$4\ CH_3C_6H_4NH_2$	$C_6H_5CH_3$	$o > p$	G	(134)
$4\text{-}BrC_6H_4NH_2$	$C_6H_5CH_3$	$o > p$	G	(134)
$4\text{-}NH_2C_6H_4C_6H_5$	$C_6H_5CH_3$	$o > p > m$	H	(117)
$(C_6H_5COO)_2$	$C_6H_5CH_3$	p	P	(106, 212)
$C_6H_5NH_2$	$m\text{-}C_6H_4(CH_3)_2$	$(o, p)^*$	G, H	(141)
$C_6H_5NH_2$	$s\text{-}C_6H_3(CH_3)_3$		G, H	(141, 158)
$C_6H_5NH_2$	$C_6H_5OCH_3$	$o > p$	G	(108)
$4\text{-}BrC_6H_4NH_2$	$C_6H_5OCH_3$	$o > p$	G	(149)
$4\text{-}IC_6H_4NH_2$	$C_6H_5OCH_3$	o, p	G	(149)
$3\text{-}O_2NC_6H_4NH_2$	$C_6H_5OCH_3$	$o > p$	G, H, D	(108)
Methyl 4-aminophthalate	$C_6H_5OCH_3$	o, p	G	(46)
$4\text{-}NH_2C_6H_4C_6H_5$	$C_6H_5OCH_3$	o, p	H	(117)
$C_6H_5NH_2$	$C_6H_5COOCH_3$	p	G	(133)
$C_6H_5NH_2$	$C_6H_5COOC_2H_5$	p, o, m	G	(141, 159)
$(C_6H_5COO)_2$	$C_6H_5COOC_2H_5$	p, m	P	(159)
$(3\text{-}O_2NC_6H_4COO)_2$	C_6H_5COOH	p, m	P	(173)
$C_6H_5NH_2$	C_6H_5CHO	p	H	(141)
$C_6H_5NH_2$	C_6H_5CN	p	G	(133)
$C_6H_5NH_2$	$2\text{-}O_2NC_6H_4CH_3$	p to NO_2	G, H	(141)
$C_6H_5NH_2$	C_5H_5N	α, γ	D	(233)
$C_6H_5NH_2$	C_5H_5N	$\alpha > \beta > \gamma$	G, H	(111, 151, 152)
$C_6H_5NH_2$	C_5H_5N	α, γ	D	(293–297)
$r\text{-}O_2NC_6H_4NH_2$	C_5H_5N	$\alpha > \beta > \gamma$	G, D	(111, 178)
$4\text{-}ClC_6H_4NH_2$	C_5H_5N	α, γ	G	(45)
$\left\{\begin{matrix}4\text{-}\\3\end{matrix}\right.NH_2C_6H_4C_6H_5$	C_5H_5N	α, γ	G	(156)
β-Naphthylamine	C_5H_5N	α, β, γ	D	(111)
4-Aminophthalimide	C_5H_5N	α, β, γ	D	(111)
$4\text{-}C_2H_5OC_6H_4NH_2$	C_5H_5N	α, γ	G	(45)
$4\text{-}HOOCC_6H_4NH_2$	C_5H_5N	α, γ	G	(45)
$(C_6H_5COO)_2$	C_5H_5N	α, γ	P	(114)
$(C_6H_5COO)_2$	C_5H_5N	$\alpha > \beta, \gamma$	P	(173, 237)
$(r\text{-}O_2NC_6H_4COO)_2$	C_5H_5N	No reaction	P	(173; *cf.* 63)
$(4\text{-}ClC_6H_4COO)_2$	C_5H_5N	α, γ	P	(173)
$(4\text{-}CH_3OC_6H_4COO)_2$	C_5H_5N	α, γ	P	(173)

TABLE 3—*Concluded*

Reagent (Ar′• Producer)	Solvent ArX	Substitution	Reaction	Reference
$(2\text{-}C_{10}H_7COO)_2$	C_5H_5N	α, β, γ	P	(173)
$C_6H_5NH_2$	C_6H_5OH	*p* > *o*	G	(64, 178)
$C_6H_5NH_2$	C_6H_5OH	*p*	G	(56, 57)
$C_6H_5NH_2$	$2\text{-}CH_3C_6H_4OH$	*p* to OH	G	(56, 57)
Anthranilic acid	C_6H_5OH	*o* > *p*	G	(135)
$\left\{\begin{matrix}4\text{-}\\6\text{-}\end{matrix}\right.$Chloroanthranilic acid	C_6H_5OH	*o*	D	(193)
$C_6H_5NH_2$	$C_6H_5NH_2$	*p*, *o*	G	(179)
$C_6H_5NH_2$	$C_{10}H_8$	1 > 2	H	(192)
$C_6H_5NH_2$	$C_{10}H_8$	1 > 2	G	(232, 284)
$C_6H_5NH_2$	$2\text{-}CH_3C_{10}H_7$	1	H	(192)
$C_6H_5NH_2$	$2,6\text{-}(CH_3)_2C_{10}H_6$	1	H	(192)
$C_6H_5NH_2$	$2\text{-}C_2H_5OC_{10}H_7$	1 > 3 > 6	H	(192)
Methyl anthranilate	$2\text{-}CH_3OC_{10}H_7$	1	D	(111)
Methyl anthranilate	$C_{10}H_8$	1	G	(142)
$C_6H_5NH_2$	$C_6H_5C_6H_5$	*p*	D	(232)
$C_6H_5NH_2$	$C_6H_5C_6H_5$	*p*	G	(142)
$4\text{-}O_2NC_6H_4NH_2$	$C_6H_5C_6H_5$	*p*	G	(142)
4-Anisidine	$C_6H_5COC_6H_5$	*p*	G	(142)

* Letters *o*, *p* in parentheses indicate substitution ortho to one group in the solvent and para to the other.

pendent reaction has some probability of occurrence, the final product is often complex and intractable. Highly substituted compounds such as quaterphenyl (1, 5, 122, 125, 174) are sometimes present and tars are usually formed. Since these tars and resins have often been ignored, the isolated yield, represented by the biphenyl fraction, has been low and subject to uncertainty (*cf.* Dermer and Edmison (92, table 2)).

(ii) In the prepared biphenyl fraction, the para isomer, being the most symmetrical, is usually the least soluble and most easily crystallized and is, therefore, the isomer most readily identified. This gave rise to the concept of para reaction, noted above. As pointed out by Hey (160) in 1948, the predominance of the ortho isomer in reactions with anisole is significant, and it may be seen from table 3 that this is also true of toluene (299).

(iii) The reactions have most often been used (7) solely as a means of preparing the *p*-arylated compounds ArAr′, and residues have been discarded without identification.

In table 3 the columns give, in order, the reactants, i.e., the producers of Ar′• radicals (in this column *r*-$NO_2C_6H_4NH_2$, for example, indicates that all three nitroanilines were used with similar results); the solvents ArH (usually C_6H_5X, where X is the directing group); the position of substitution relative to the directing group; the type or types of reaction; and the appropriate literature references. In designating the reaction the scheme above is used.

Where possible the isomer formed in greatest yield is indicated. This information should, however, be treated with caution for the reasons stated above.

Table 3 is not fully comprehensive. It does not include the work carried out on furan, thiophene (133), or quinoline (173), which is small in quantity and not directly relevant. The results receive confirmation from other work: e.g., (*1*) the electrolysis of benzoic acid in pyridine (114) gives α- and γ-phenylpyridines, and (*2*) the decomposition of diphenyliodonium hydroxide in pyridine (253) yields all three isomers. (See references 131, 164, 253, and 299; also Section VI,A.)

Consideration of table 3 confirms a mode of substitution different from the normal ionic one and suggests invariable ortho–para-directing effects for the group X. It is necessary to turn to the years since 1951 to see how these ideas have become modified.

IV. THEORETICAL ASPECTS OF AROMATIC SUBSTITUTION

A. INTRODUCTION

In order to orientate the theoretical aspects of free-radical substitution with those for ionic substitution it is necessary to present the development of the various treatments and the relationships between them.

Any reaction involving a given molecule can be described (41, 70, 130) by a reaction path ABC (figure 1), wherein an energy barrier, the height of which is equal to the energy of activation, has to be surmounted in the process of movement along the reaction coordinate towards the reaction product C. In order to predict the relative rates of reaction at two sites, it is necessary to possess a means of evaluating both the reaction paths ABC and A'B'C'. Owing to inherent difficulties of calculation, it is usually impossible to carry out these estimations

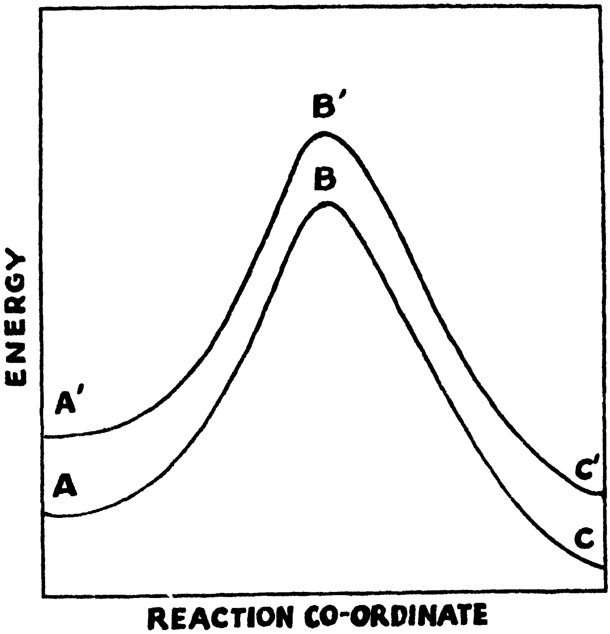


FIG. 1. Reaction paths for a given molecule

rigorously, and certain assumptions have to be made in order that some result may be obtained. In heterolytic reactions the electrically charged entities taking part in the reaction engage in strong long-range Coulombic interaction and here, therefore, the electrical charge distribution in the initial molecule (A, figure 1) plays the dominant role and decides the products of the reaction. It will be remembered that the early experimental data were concerned only with heterolytic substitutions (Section II), and thus the earlier theoretical treatments describe this form of reaction alone, i.e., they are concerned with a description of the charged ground state of the molecule. Unfortunately, the perturbations caused by approach of the electrically charged reagent to the molecule produce difficulties in mathematical description of the reaction and these early treatments were not able to progress far towards a truly quantitative understanding of aromatic substitution as it was then known.

In homolytic reactions, on the other hand, where the electrical perturbations are small, the order of reactivity of a number of given positions might be described by a sequence of "residual affinities." Any atom in a lower order of bonding would then, because of its "residual affinity," be more amenable to reaction than any other atom. This implies that the differences in energies between the initial molecules and certain ideal states determine the reaction products and that the order of relative rates is independent of the attacking reagent.

From the above it follows that a broad classification of the topic may be made and three groups of theories are distinguished:

(i) Methods involving consideration of the electrical charge configurations of the isolated molecules A, referring qualitatively to heterolytic reactions.
(ii) Methods based on the evaluation of the aforementioned "residual affinities" which are applicable, not only qualitatively but probably quantitatively, to homolytic reactions.
(iii) Methods based on the possibility of calculating, for each type and position of reaction, the energy of activation or the height of the energy barrier (AB, figure 1) involving the corresponding activated complex. These results are applicable, in a quantitative sense, to both homolytic and heterolytic substitution.

It is customary to consider (i) and (ii) together, as the "isolated molecule" (I.M.) method of approach, and (iii) separately as the transition state (T.S.) method (41, 54, 70, 73, 74, 76, 100–105, 136, 137). Thus, the first treatment considers the reaction path in the neighborhood of A (figure 1) and involves the assumptions that the outcome of the reaction is decided by the molecule itself and that the relative positions of A and A′ decide the relative rate of reaction between the two positions considered. The second method, on the other hand, is concerned with the relative heights AB, A′B′ of the corresponding reaction paths.

B. GENERAL ASSUMPTIONS OF THE ISOLATED MOLECULE (I.M.) AND TRANSITION STATE (T.S.) METHODS

The general methods, assumptions, and equations used in the I.M. and T.S. treatments and in the interpretation of experimental results must now be considered.

1. Since the mobile p-π electrons in aromatic systems are more easily polarized, and are also delocalized over a much larger area than the σ-bond electrons, the contribution of the latter to the variable part of the activation energy may be ignored. Thus, each theory operates on the p-π electrons alone and the σ-bond effects are assumed negligible.

2. At the present stage, the complicating effects of steric hindrance are assumed absent. These effects can only be explained qualitatively in systems of this complexity and must be left untreated in any current mathematical appreciation. Likewise, experimental data which are free of the uncertainty arising from steric effects must be used in testing the theoretical work.

3. For any reaction, the theory of absolute reaction rates (130), in considering the reaction path of figure 1, indicates that the rate of reaction is

$$k \propto e^{\Delta S^{\ddagger}/R} \cdot e^{-\Delta H^{\ddagger}/RT} \tag{26}$$

If the entropy of reaction $\Delta S^{\ddagger}$ is incorporated into the frequency factor P, and if $\Delta H^{\ddagger}$, the heat of activation, is replaced by the energy of activation ΔU (AB, figure 1), the equation degenerates (70) to that of Arrhenius:

$$k = Pe^{-\Delta U/RT} \tag{27}$$

The reasonable assumption is now made that in a series of similar reactions, employing similar molecules in reaction with a stated reagent, the entropy term $\Delta S^{\ddagger}$ and/or the frequency factor P remains constant. This has been observed to be true in many instances (27, 34–40, 200, 201, 246). Thus, the application of equation 27, with the replacement of the term ΔU by an energy difference evaluated by any of the theories, should allow the corresponding value of k to be obtained.

4. If ${}^{\mathrm{H}}k$ and ${}^{\mathrm{X}}k_r$ represent actual rates of reaction for any position in benzene and the position r in C_6H_5X, respectively, then two equations similar to equation 27 give the partial relative rate factor ${}^{\mathrm{X}}_{\mathrm{H}}k_r$ as

$${}^{\mathrm{X}}_{\mathrm{H}}k_r = {}^{\mathrm{X}}k_r/{}^{\mathrm{H}}k = \exp\left(\frac{\Delta^{\mathrm{H}}U - \Delta^{\mathrm{X}}U_r}{RT}\right) \tag{28}$$

where the terms $\Delta^{\mathrm{H}}U$ and $\Delta^{\mathrm{X}}U_r$ are the energy differences calculated for the reaction using C_6H_6 and the r^{th} position of C_6H_5X, respectively.

5. Consider predictions made by the I.M. and T.S. methods for heterolytic substitution. The former treatment assumes that the course of the relative reaction for two different sites or compounds may be predicted from a knowledge of the distribution of the ground state charges alone. The T.S. method, which

involves evaluation of the corresponding energies of activation (figure 1), might predict a reverse order of reactivity if the reaction paths for the different sites or compounds crossed. A review which includes a discussion on the effects of such crossing has recently been published (41). The following generalizations may be made:

(i) The possibility of crossing is greatest for the ionic reactions where time-variable perturbation effects, dependent on the Coulombic interaction between the reagents, are present. Qualitative considerations are introduced into the theories to allow for this (Section IV,C,1).

(ii) Reliance may be placed on the prediction for heterolytic substitution if the results of both I.M. and T.S. methods agree.

(iii) Homolytic substitution is decided by energy-difference relationships (Section IV,A), and therefore the predictions of the I.M. and T.S. methods might be expected to be in agreement and to have more significance than those for heterolytic reactions. Such an agreement will become apparent at a later stage (Section IV,C,5; Section IV,D,2).

6. Partial and total rate factors relative to benzene are obtained as follows (21): If the absolute reaction rates are considered, then for substitution of C_6H_5X, where there are two ortho positions, two meta positions, and one para position available for reaction, the total absolute rate is given by:

$$^{\mathrm{X}}K = 2\,^{\mathrm{X}}k_o + 2\,^{\mathrm{X}}k_m + {}^{\mathrm{X}}k_p \tag{29}$$

For benzene, with six equivalent positions, the corresponding rate is

$$^{\mathrm{H}}K = 6\,^{\mathrm{H}}k \tag{30}$$

By measuring relative total rate ratios, an arbitrary value may be assigned to one compound so that numerical significance may be given to the other terms. Benzene is taken as the reference molecule and the total rate of substitution in benzene (equation 30) is taken to be equal to six, whereby $^{\mathrm{H}}k$ is unity. From equations 29 and 30 we then have:

$$6\,^{\mathrm{X}}_{\mathrm{H}}K = 2\,^{\mathrm{X}}_{\mathrm{H}}k_o + 2\,^{\mathrm{X}}_{\mathrm{H}}k_m + {}^{\mathrm{X}}_{\mathrm{H}}k_p \tag{31}$$

The value of $^{\mathrm{X}}_{\mathrm{H}}K$ can be measured experimentally by the competitive method, using mixtures of C_6H_5X and C_6H_6.

The partial relative rate factors $^{\mathrm{X}}_{\mathrm{H}}k_r$ are obtained if the proportions in which the isomers are formed are measured; thus, if the ortho isomer forms the fraction (*o*) of the product mixture, then:

$$\left.\begin{aligned} (o) &= \frac{2\,^{\mathrm{X}}_{\mathrm{H}}k_o}{2\,^{\mathrm{X}}_{\mathrm{H}}k_o + 2\,^{\mathrm{X}}_{\mathrm{H}}k_m + {}^{\mathrm{X}}_{\mathrm{H}}k_p} \\ \text{i.e.,}\qquad {}^{\mathrm{X}}_{\mathrm{H}}k_o &= 3\,^{\mathrm{X}}_{\mathrm{H}}K(o) \end{aligned}\right\} \tag{32}$$

Similar equations can clearly be derived for the meta and para cases, due allowance being made for the statistical number of these positions available for reaction. The process is likewise extended to the treatment of molecules like biphenyl, naphthalene, etc.

Several very important points arise from these considerations:

(i) The rate ratio ${}^{\mathrm{X}}_{\mathrm{H}}K$ may be obtained (1) indirectly by experiments using a third substance, e.g., C_6H_5Y, since

$$ {}^{\mathrm{X}}_{\mathrm{H}}K = {}^{\mathrm{Y}}_{\mathrm{H}}K \cdot {}^{\mathrm{X}}_{\mathrm{Y}}K \tag{33}$$

Thus, once the value of ${}^{\mathrm{Y}}_{\mathrm{H}}K$ is established, the molecule C_6H_5Y can be used as the experimental reference compound and competitive work may be carried out by using mixtures of C_6H_5X and C_6H_5Y rather than mixtures of C_6H_6 and C_6H_5X. This may be desirable on account of a possible simplification of the experimental procedure. Moreover, by comparing the directly determined value of ${}^{\mathrm{X}}_{\mathrm{H}}K$ with that obtained by the use of equation 33, a check on the experimental accuracy may be obtained.

(ii) If, from calculations based on any theory, the total reaction rate is desired, then equation 31 must be employed, i.e., the individual partial rate factors ${}^{\mathrm{X}}_{\mathrm{H}}k_r$ are obtained, perhaps by equation 28, and are summed by the use of equation 31. This follows from the Arrhenius equation (equation 27), which shows that addition of energy terms, appearing as indices in the exponential, leads to multiplication rather than addition of the rate constants. Thus, for example, it is not allowable (176) to employ the summation of the free valence numbers for the various positions in a molecule in order to assess the total reactivity of the molecule [see Sections IV,C,5,(iii) and V,B,6]. This comment applies rigorously to all cases, even those where one or two positions have very largely enhanced reactivities, e.g., in the polynuclear hydrocarbons (205, 206).

7. If *p*-diX-substituted, or *s*-triX-substituted benzene is considered (5), then, for both instances, all the nuclear positions available for substitution are equivalent, e.g., for *p*-diX-substituted benzene, any position is ortho to one X and meta to the other X group; hence,

$$ 6\,{}^{p\text{-}\mathrm{X}_2}_{\ \ \mathrm{H}}K = 4\,{}^{p\text{-}\mathrm{X}_2}_{\ \ \mathrm{H}}k_{o,m} \tag{34}$$

where the subscript *o,m* indicates that the relative rate for this individual position has some dependence on the positions of the two directing X groups.

It has been shown for heterolytic substitution and for some homolytic reactions (21, 27, 200, 201, 246) that the effect of the substituent is concerned mainly with the energy of activation for reaction at any position in the nucleus, i.e., it may be assumed that the frequency factor, *P* in equation 27, will remain sensibly constant in the competitive reaction involving either C_6H_5X or *p*-diX-benzene. This was seen to be a requirement for the validity of the competitive method (see Sections IV,B,3 and IV,B,4).

The experimental evidence shows that the energy of activation at an available position is formed by addition of the corresponding energies of activation contributed by all the directing groups. If this is true of homolytic substitution reactions, then noting from (ii) above that addition of activation energies implies multiplication of rate constants, the partial rate factor ${}^{\mathrm{X}}_{\mathrm{H}}k_{o,m}$ from equation 34 is given by the product of ${}^{\mathrm{X}}_{\mathrm{H}}k_o$ and ${}^{\mathrm{X}}_{\mathrm{H}}k_m$, where each of these latter factors corresponds to the effect produced at the attacked position r by one of the X groups, either ortho or meta to r. Hence,

$$ {}^{\mathrm{X}}_{\mathrm{H}}k_{o,m} = {}^{\mathrm{X}}_{\mathrm{H}}k_o \cdot {}^{\mathrm{X}}_{\mathrm{H}}k_m \tag{35} $$

and

$$ 6\,{}^{p\text{-}\mathrm{X}_2}_{\mathrm{H}}K = 4\,{}^{\mathrm{X}}_{\mathrm{H}}k_o \cdot {}^{\mathrm{X}}_{\mathrm{H}}k_m $$

Similar considerations are valid for *s*-triX-benzene, where each nuclear position is ortho to two X groups and para to the third, i.e.,

$$ 6\,{}^{s\text{-}\mathrm{X}_3}_{\mathrm{H}}K = 3({}^{\mathrm{X}}_{\mathrm{H}}k_o)^2\,{}^{\mathrm{X}}_{\mathrm{H}}k_p \tag{37} $$

From the experimental values of ${}^{\mathrm{X}}_{\mathrm{H}}K$, ${}^{p\text{-}\mathrm{X}_2}_{\mathrm{H}}K$, ${}^{s\text{-}\mathrm{X}_3}_{\mathrm{H}}K$, the three unknowns ${}^{\mathrm{X}}_{\mathrm{H}}k_o$, ${}^{\mathrm{X}}_{\mathrm{H}}k_m$, and ${}^{\mathrm{X}}_{\mathrm{H}}k_p$ may be obtained by solution of a cubic equation derived from equations 31, 36, and 37. If these values agree with those obtained using the data of the isomer proportions and ${}^{\mathrm{X}}_{\mathrm{H}}K$ (equation 32), then the postulate of the additivity of activation energies will be verified. It is to be noted that this method assumes the absence of steric hindrance (see Section IV,B,2).

8. The effect of temperature upon the relative rates and isomer proportions may be evaluated by consideration of equations 27, 28, 31, and 32. It is clear that the effect can be observed directly only via the partial rate factors ${}^{\mathrm{X}}_{\mathrm{H}}k_r$, and not through the total rate values ${}^{\mathrm{X}}_{\mathrm{H}}K$. The effect on the latter can be found, however, by finding the changes in the ${}^{\mathrm{X}}_{\mathrm{H}}k_r$ values and employing equation 31. Using the Arrhenius equation, equations 27 and 28, and the temperatures T_1 and T_2, we have:

$$ ({}^{\mathrm{X}}_{\mathrm{H}}k_{r,T_2}) = ({}^{\mathrm{X}}_{\mathrm{H}}k_{r,T_1})^{T_1/T_2} \tag{38} $$

Further, by inclusion of equation 32 and putting $T_1/T_2 = \eta$, the relationships between the isomer proportions are given by equations of the form:

$$ (o)_{T_2} = \frac{2\left(\frac{o}{2}\right)^{\eta}}{\left[2\left(\frac{o}{2}\right)^{\eta} + 2\left(\frac{m}{2}\right) + (p)\right]_{T_1}} \tag{39} $$

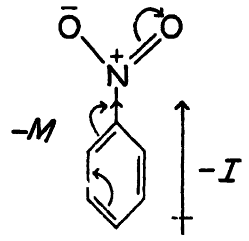
By these and similar relationships, the partial rate factors, isomer proportions, and total rate factors may be obtained at any temperature. The inherent assumption that has been made is that the P-factor remains constant (see Section IV,B,3).

C. ISOLATED MOLECULE (I.M.) APPROACH

Each of the following theories represents an attempt to describe substitution phenomena. In each case, the possibility of application to homolytic substitution is discussed. It will be seen that the first three methods described are applicable mainly to heterolytic substitution, while the last two have been developed specifically for the free-radical reactions.

1. *Ideas of the English School*

The electronic interpretation by the English School (8, 21, 194, 196–198, 246) of the "normal laws" of substitution (see Section II) is as follows: In general, according to the classification of group X, the group is assigned a ± *I* (inductive) and a ± *M* (mesomeric) effect. Thus, the NO_2 group is said to exert the effects $-I$, i.e., withdrawal of electrons from the ring by a mechanism analogous to electrostatic induction, and $-M$, i.e., withdrawal of electrons by the tautomeric mechanism. Both mechanisms affect the ortho and para positions to a greater extent than the meta position and, in this sense, the tautomeric mechanism is considerably the more selective. The result, in nitrobenzene (I), for example,



I

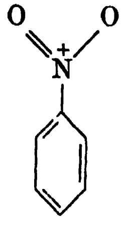
is such that an electrophilic reagent (e.g., NO_2^+) finds difficulty in attacking the ortho and para sites, and so the NO_2 group is said to be deactivating and meta directing.

In some cases the approach of the reagent causes electrical perturbation of the molecule with consequent modification of the expected results. Time-variable effects—namely, the $\pm I_d$ (inductomeric or dynamic inductive) and $\pm E$ (electromeric) effects—were therefore postulated to allow for this. These effects are called into play only on the demand of the approaching reagent, and thus they can only aid reaction and never inhibit it.

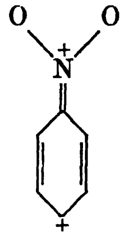
These descriptions are essentially qualitative and unable to explain free-radical substitution effects (Section II).

2. *Resonance theory*

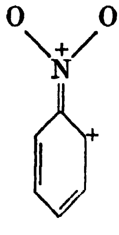
Directing effects observed in ionic substitution are explained by the charge distribution existing in a hybrid molecule constructed by the summation of contributions from a number of separate canonical forms, which can be represented by classical valence-bond formulae (239, 291). Thus, for example, for nitrobenzene the following structures (II, III, and IV) are among those which contribute to the hybrid structure.



II



III



IV

The structures indicate that electrophilic substitution (for example, by NO_2^+) will be rendered more difficult compared with benzene, and the substituent will be directed to the meta position.

The theory is capable of mathematical treatment (48, 54, 88) by the valence-bond method but has served mainly as a means of semiquantitative description of heterolytic reactions. In the form presented, the method is inapplicable to free-radical substitution, but with certain modifications (Sections IV,C,4 and IV,D,1) can attempt such description.

3. *Molecular orbital (M.O.): the polarized state*

This treatment, which was developed in an attempt to explain the facts of heterolytic substitution, departs somewhat from the strict I.M. procedure, since points slightly displaced from A (figure 1) are considered (41, 70, 73, 74, 130, 292). If an ion, e.g., NO_2^+, approaches a molecule at position r, electrons will tend to congregate at this site. This results in a decrease in the electronegativity of r and a change in the Coulomb integral of the carbon atom occupying position r from α_r to $(\alpha_r + \delta\alpha_r)$, where $\delta\alpha_r$ is negative. The resulting change, δU, in the energy of the system is given by a Taylor series of the form:

$$
\begin{aligned}
\delta U &= \frac{(\partial U)}{(\partial \alpha_r)} \delta\alpha_r + \frac{1}{2} \frac{(\partial^2 U)}{(\partial \alpha_r^2)} \delta\alpha_r^2 + \\
&= q_r \cdot \delta\alpha_r + \tfrac{1}{2}\pi_{r,r}(\delta\alpha_r)^2 +
\end{aligned}
\qquad (40)
$$

where the quantity q_r is termed the *π-electron charge density* and $\pi_{r,r}$ the self-polarizability of the r^{th} carbon atom. It is to be noted that this assumes that long-range Coulombic forces are dominant and exchange forces are not present. If these latter forces were engaged, then equation 40 should contain terms like $\partial U/\partial\beta_{rs}$ to allow for effects brought about by changes in the bonding of the r^{th} carbon atom.

The first term in equation 40 is the most important and, since $\delta\alpha_r$ is negative, the most reactive position for heterolytic substitution is that where q_r is largest, i.e., that of the greatest electronic charge. This is in accord with the above treatments, in all of which the charge distribution in the ground state determines the products.

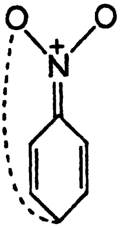
If all the q_r's are identical (e.g., in unsubstituted hydrocarbons like naphthalene), the difference in reactivity is given by the second term involving $(\delta\alpha_r)^2$.

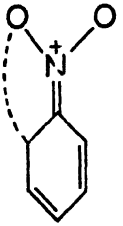
In this instance, the substitution depends only on the magnitude and not on the sign of $\delta\alpha_r$. Hence, both electrophilic and nucleophilic substitution will take place preferentially at the same site.

If all the quantities of equation 40 were known, including bonding terms, then some attempt might be made to obtain the corresponding partial rate factors by means of equation 28. The difficulties involved in carrying out such calculations are, however, prohibitive. The method is important in treating the electron configuration as a whole by mathematical argument, and the inherent inclusion of the polarizability effects is significant. The experimental facts can be explained in a qualitative sense but quantitative prediction cannot be made.

4. *Valence libre*

This concept, which was developed by French theorists (48, 54, 85–88, 244, 245) from an idea of Svartholm (270), was an attempt to adapt the resonance theory (Section IV,C,2) to the treatment of homolytic substitution. Since canonical forms containing electrical charges in the nucleus are of no apparent importance in free-radical reactions, these structures, which occur in the normal resonance theory (formulas II, III, and IV), are replaced by structures bearing formal bonds (formulas V and VI). The "valence libre" of a given atom is then defined as the weighted sum of all structures in which the chosen atom is not joined by a double bond to one of its neighbors. Some possible structures for nitrobenzene are shown in formulas V and VI, wherein the ortho and para positions are the only ones for which formal-bond structures of this type can be written. Structures containing more than one such bond, when suitably weighted, are included in the treatment. The total weight of these structures for a given atom is then a measure of the residual affinity of the atom concerned. The weighting is carried out by using suitable experimental data referring to bond lengths (48, 245). The structures (V and VI) for nitrobenzene show that preferential ortho–para reaction should take place in homolytic substitution.


V


VI

The treatment has been applied (245) to linear and condensed polynuclear hydrocarbons and appears satisfactory in explaining the reactivities of selected positions and the corresponding carcinogenic activity of such compounds. No calculations for the case of a monosubstituted benzene (C_6H_5X) have been published except for an attempt to treat toluene (245). It is doubtful whether the method should be applied to heteromolecules (99). The treatment suffers from its rather pictorial approach (99, 232).

An interesting point, which does not appear to have been expressed, is that whatever the nature of the group X, provided there is some conjugation or hyperconjugation with the benzene ring, the ortho and para positions will always appear more reactive than the meta position in homolytic substitution, owing to the inclusion of structures of the type illustrated in formulas V and VI. Moreover, since these structures are additional to any containing formal bonds within the benzene ring itself (e.g., the Dewar structures), the treatment suggests that homolytic attack should be facilitated, relative to benzene, by the presence of the group X in the molecule C_6H_5X. If conjugation is small as, for example, in *tert*-butylbenzene, this activating effect should be of minor importance (see Section VII,A,4,(v)).

5. *Free valence*

The idea of free valence was introduced by Coulson (68, 69). Using the molecular orbital (M.O.) theory, the mobile bond order p_{rs} between the nuclear carbon atoms r and s is defined by

$$p_{rs} = \Sigma c_{rj} c_{sj} \tag{41}$$

where c_{rj} and c_{sj} are the coefficients of the molecular orbitals of the electrons in the bonds r–j and s–j. The total bonding N_r exhibited by the atom r is then

$$N_r = \Sigma p_{rs} + C_r \tag{42}$$

where C_r is the contribution from the σ-electrons. The free valence, F_r, of r is then given by

$$F_r = (N_{\max} - N_r) \tag{43}$$

where $N_{\max}$ is the maximum bonding that a carbon atom of the type r can attain (76, 136, 137). The value of $(N_{\max} - N_r)$ is a measure of the amount of additional bonding which this atom r could show and provides an index for homolytic reactivity.

Each reactivity is associated with the difference between a fixed bonding value, calculated for the initial molecule (A, figure 1), and that idealized maximum of which the carbon atom concerned is capable. This change F_r in bonding must be associated with a corresponding energy difference, $({}^{X}E'_r - {}^{X}E')$, where ${}^{X}E'$ and ${}^{X}E'_r$ are the π-electron energies of the corresponding initial and r-substituted molecules. This difference may be taken as determining $\Delta^{X}U_r$ in equation 28. (It is the evaluation of this energy difference which suggests a parallelism with the method of Wheland (see Section IV,D), where the energy difference between the ground state and the transition complex is calculated.)

A qualitative relationship between ${}^{X}F_r$ and $\Delta^{X}U_r$ has been demonstrated by Burkitt, Coulson, and Longuet-Higgins (44: *cf.* 143). The contribution of atom r to the mobile electron energy of a system can be shown to be $2\beta\Sigma p_{rs}$. If, during the course of a reaction, it is assumed that this atom is removed from the area of delocalization, then the energy change will have this value $2\beta\Sigma p_{rs}$, provided there is no rearrangement of the rest of the molecule. (This system may be compared with the activated complex of Wheland, where a covalent bond is assumed to be formed between the radical and the atom attacked.) Thus, taking β as positive:

$$\Delta^{X}U_r = ({}^{X}E'_r - {}^{X}E') = 2\beta\Sigma p_{rs} = 2\beta(N_r - C_r) \tag{44}$$

$$= 2\beta[N_{\max} - C_r - {}^{X}F_r]$$

$$= \text{constant} - 2\beta F_r \tag{45}$$

This equation is a mathematical statement of the fact that the greater the free valence available the greater the reactivity, since the larger ${}^{X}F_r$, the smaller $\Delta^{X}U_r$ and, by equation 28, the more reactive the position.

The rest of the molecule cannot remain unaffected when atom r is removed from the delocalization area and all the other mobile bond orders p_{mn} must change. Relationship 45 will therefore be correct only if the sum of these changes is zero. Brown (41) uses a modified equation:

$$\Delta^{X}U_r = \text{const.} - 2x\beta^{X}F_r \tag{46}$$

where $x\beta$ is a similar change in all the resonance integrals β_{rs} between atom r and its neighbor s, and where $0 \leq x \leq 1$.

Using calculated bond orders in conjunction with equations 41–43, the partial rate factors may be evaluated by equation 28. Thus,

$$^{X}_{H}k_r = \exp 2(x)\beta \frac{({}^{X}F_r - {}^{H}F)}{RT} \tag{47}$$

Tables 4 and 5 present some of the data, together with the calculated values of ${}^{X}F_r$, ${}^{X}_{H}k_r$, and ${}^{X}_{H}K$ (see Section IV,B).

It is seen that:

(i) The $({}^{X}F_r - {}^{H}F)$ values are very small, causing the predicted rates to

TABLE 4

Free valence numbers ${}^{X}F_r$

Aromatic Compound	Nuclear Position†			References
	Ortho or α	Meta or β	Para or γ	
C_6H_6	0.398	0.398	0.398	(73, 176, 254)
C_6H_5F	0.412	0.398	0.404	(254)
C_6H_5Cl	0.410	0.400	0.404	(254)
C_6H_5Br	0 413	0.400	0.404	(254)
C_6H_5I	0.432	0.397	0.412	(254)
C_6H_5OH	0.422	0.395	0.406	(254)
$C_6H_5NH_2$	0.431	0.396	0.412	(254; *cf.* 74)
C_5H_5N	0.420	0.394	0.412	(254)
C_5H_5N*	0.405	0.390	0.454	(74, 76)
$C_{10}H_8$	0.448	0.400	—	(254)
[illegible]	0.452	0.404	—	(44, 74, 76)
$C_6H_5C_6H_5$*	0.436	0.395	0.412	(44; *cf.* 256, 257)

* See Section IV [illegible],5, (iv).

† These values are calculated using $N_{\max} = 3 + \sqrt{3}$ (equation 43). Provided the same value for $N_{\max}$ is used in all the calculations its actual value is unimportant, as the difference $({}^{X}F_r - {}^{H}F)$ is used (equation 43) to calculate the relative rates given in table 5.

TABLE 5

Homolytic relative rate constants calculated from free valence numbers, assuming $x = 1$, $T = 353°K.$, $\beta = 17$ *kcal.* (*equations 44–47*)

Compound	${}^{X}_{H}k_o$ or ${}^{X}_{H}k_\alpha$	${}^{X}_{H}k_m$ or ${}^{X}_{H}k_\beta$	${}^{X}_{H}k_p$ or ${}^{X}_{H}k_\gamma$	${}^{X}_{H}K$
C_6H_5F	1.97	1.00	1.34	1.21
C_6H_5Cl	1.79	1.10	1.34	1.19
C_6H_5Br	2.07	1.10	1.34	1.28
C_6H_5I	5.12	0.95	1.97	2.35
C_6H_5OH	3.20	0.91	1.97	1.70
$C_6H_5NH_2$	4.95	0.91	1.97	2.28
C_5H_5N	2.91	0.82	1.97	1.57
C_5H_5N*	110.25	0.02	15.11	39.28
$C_{10}H_8$	11.29	1.10	—	8.26
$C_{10}H_8$	13.71	1.34	—	10.03
$C_6H_5C_6H_5$*	804.95	0 86	1.97	538.53

* See Section IV,C,5,(iv)

be highly subject to the accuracy of evaluation of the individual F_r values.

(ii) The possible fluctuation of the value of x in equations 44–47 and, indeed, the questionable validity of these equations, implies that no great reliance should be placed in the ${}^{X}_{H}k_r$ figures. Strictly, this also applies to any qualitative predictions based on ${}^{X}F_r$ values for positions within a single molecule for unless, in every case, the rest of the molecule either remains unchanged or alters to the same degree (i.e., $x = 1$ or is constant) during the reaction, the ${}^{X}F_r$ sequence cannot be assumed to indicate the order of reactivities. In the past these assumptions have been rather too readily accepted.

(iii) The dangers inherent in taking the summations of the ${}^{X}F_r$ values (176) for comparing reactivities of molecules [see Section IV,B,6,(ii)] are demonstrated for the halogens. Thus, addition of the ${}^{X}F_r$ values leads to the incorrect order of "reactivities" I > Br > Cl > F when compared with the sequence given by ${}^{X}_{H}K$ of table 5. These orders should be compared with those for heterolytic reactions (222).

(iv) The values for pyridine, naphthalene, and biphenyl are important, as the corresponding calculations can be made with some accuracy. There is no heteroatom in naphthalene, and consequently no arbitrary parameter need be introduced when calculating ${}^{X}F_r$ or, alternatively, to calculate ${}^{X}F_r$. It is noticed in these cases that the ortho positions give rise to very high values. Experimentally, these may not be observed, owing to steric hindrance at ortho sites. The values marked with an asterisk in tables 4 and 5 seem out of harmony, perhaps owing to the neglect of overlap integrals, and are rejected.

(v) In all the cases quoted in tables 4 and 5 it is seen that the ortho and para positions are activated to a greater degree than the meta position, which, having an ${}^{X}_{H}k_m \sim 1.0$, is little different from any one position in benzene. The effect is an alternation in reactivity round the ring from the group X. Approximate treatment (76, 136) has shown the possible reason for this selected activation. A hydrocarbon molecule is considered, e.g., benzene, and the Coulomb term α_s of one atom s is changed; [this may be considered as being effected by replacement of a =CH group by a hetero =N atom or by the influence of group X on s]. Neglecting any changes in the values of the bond integrals, the change in the bonding N_r of atom r is given by

$$\frac{dN_r}{d\alpha_s} \quad \frac{\partial N_r}{\partial \alpha_s} d\alpha_s + \frac{1}{2} \frac{\partial^2 N_r}{\partial \alpha_s^2} (d\alpha_s)^2 + \tag{48}$$

The first, and any other odd term, can be shown to be zero, and thus:

$$\frac{dN_r}{d\alpha_s} \sim \frac{1}{2} \frac{\partial^2 N_r}{\partial \alpha_s^2} (d\alpha_s)^2 \tag{49}$$

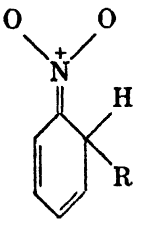
This implies that whatever the sign of $d\alpha_s$, the change in bonding of atom r will be determined by the sign of $\partial^2 N_r/\partial\alpha_s^2$. It was shown in addition that when r to s is odd, $\partial^2 N_r/\partial\alpha_s^2$ is negative and ortho and para sites are activated, and when r to s is even, $\partial^2 N_r/\partial\alpha_s^2$ is positive and meta sites are deactivated. The effects follow from the fact that a decrease in N_r causes an increase in F_r (equation 43) and hence an increase in the reactivity of atom r. The effect at the meta position is much dampened (76).

In view of the assumptions made, these results should be accepted with some reservation (75, 77), but they are nevertheless of considerable significance, as has recently been pointed out (136).

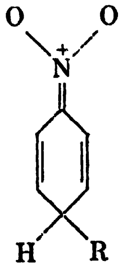
D. TRANSITION STATE (T.S.) APPROACH

1. *Resonance theory*

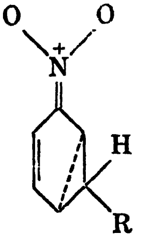
In Section IV,C,2 an account has been given of how the resonance method is applied to heterolytic substitution, and how modification of the treatment enables the subject of homolytic reactions to be treated (Section IV,C,4) Wheland (290–291), breaking away from the then current treatment of the ground state alone, suggested that the reagent–molecule relationship should be studied. Thus, the ortho-para-directing effect of X in free-radical substitution was thought to be determined by the greater ease of formation of the o- and p-R-substituted C_6H_5X molecules, compared with that of the meta compound. The



VII



VIII



IX

meta complex (IX), containing a formal bond between the ortho and para positions, should possess greater energy then the corresponding ortho (VII) and para (VIII) structures.

This method again implies (see Section IV,C,4) attack in the ortho and para positions whatever the nature of the group X, provided some conjugation or hyperconjugation with the ring exists. This approach has been employed in a recent qualitative discussion (251).

2. Atom localization energy treatment

These considerations were also initiated by Wheland (290) and have been discussed and extended by many workers (34–41, 98, 99, 260, 286). The method is an attempt to calculate the height of the potential energy barrier which has to be surmounted in order that the reaction should take place (AB, figure 1) and is known as either the transition state or atom localization energy method. The possible relation between this method and the other treatments has been discussed (Sections IV,A, IV,B, and IV,C,5). It is not the charge distribution in the initial molecule or the difference between the ground state and an idealized state of bonding, but rather the difference between the ground state and the activated complex, which decides the products.

For electrophilic, radical, and nucleophilic substitution the assumption is made that the transition state is that in which 2, 1, or 0 π-electrons, respectively, are completely localized at the point of attack *r* and are, therefore, effectively removed from conjugation. Figure 2 shows how the various quantities are derived for homolytic substitution of C_6H_5X by a radical R• at the para position. Similar diagrams can be set up for substitution at any other position of C_6H_5X. The dot represents an odd electron and the area enclosed indicates the area over which the delocalization of the *n* or $(n - 1)$ electrons takes place.

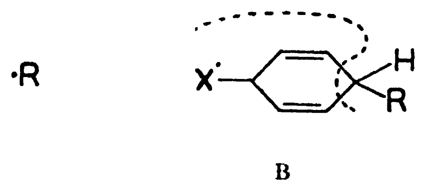


FIG. 2. Derivation of various quantities for homolytic substitution of C_6H_5X by a radical R• at the para position. (A) Ground state; energy ${}^{X}E$. Delocalization over the whole molecule of its *n* π-electrons. (B) Transition state for para substitution. Energy ${}^{X}E_p$. Restricted delocalization of the $(n - 1)$ electrons.

The π-electron energy for each of these structures may be calculated by molecular orbital methods and the difference

$$({}^{X}E_r - {}^{X}E) = {}^{X}A_r = \Delta{}^{X}U_r \qquad (50)$$

is taken to represent the variable portion of the heat of activation for the radical substitution (*cf.* Section IV,B). The atom localization energy ${}^{X}A_r$ may be

TABLE 6

Electrophilic relative reaction rate calculated from atom localization energies
(T = 291°K.)

Aromatic Compound	${}^{X}_{H}k_o$ or ${}^{X}_{H}k_\alpha$	${}^{X}_{H}k_m$ or ${}^{X}_{H}k_\beta$	${}^{X}_{H}k_p$ or ${}^{X}_{H}k_\gamma$	${}^{X}_{H}K$
NO_2	0.088	0.821	0.454	0.38
C_6H_5Cl	1.068	0.059	0.268	0.42
$C_6H_5CH_3$	42.43	13.87	34.83	24.57
C_6H_5OH	37×10^5	0.72	59×10^5	1.5×10^6
C_5H_5N	0.040	0.029	0.021	0.03
$C_{10}H$	99.2×10^4	37.2	—	4.46×10^5

identified with $\Delta^{X}U_r$ (Section IV,B) and compared with the energy difference determined by the ${}^{X}F_r$ values (Section IV,C,5, equation 44).

The method is as easily applied to heterolytic substitution, and table 6 presents the relative rate values, calculated from the published ${}^{X}E_r$ data for electrophilic substitution (290). In the calculations the bond integral was taken to be equal to -38 kcal., and the following parameters were used: ϵ_1 was included for C_6H_5Cl; $\delta_1 = 0.2$, $\delta_2 = 0.1$ for C_5H_5N, and $\delta_\alpha = -0.1$ for $C_6H_5CH_3$.

The figures in table 6 should be compared with the experimental ones of table 1, when the correspondence is seen to be rather poor. This lack of quantitative agreement was fully appreciated by Wheland. The high rate for phenol, or aniline, is predicted, but the very low values for other compounds, e.g., nitrobenzene, are not. Electrical perturbation, caused by the approach of the NO_2^+ ion, cannot account for this because this time-variable effect can only facilitate reaction (*cf.* Section IV,C,1), i.e., tend to increase the predicted figures.

For homolytic reaction, similar calculations have been made and the results are given in table 7.

Similar difficulties arise in these calculations to those already discussed (Section IV,C,5) in connection with the evaluation of free-valence numbers; e.g., the rate figures are again determined by small energy differences. The general prediction is again of slight activation with ortho-para direction. The figures for naphthalene, obtained without the use of any parameter, are very high (*cf.* table 5).

TABLE 7

Homolytic relative reaction rate calculated from atom localization energies
(T = 353°K.)

Aromatic Compound	${}^{X}_{H}k_o$ or ${}^{X}_{H}k_\alpha$	${}^{X}_{H}k_m$ or ${}^{X}_{H}k_\beta$	${}^{X}_{H}k_p$ or ${}^{X}_{H}k_\gamma$	${}^{X}_{H}K$
$C_6H_5NO_2$	2.25	0.85	8.74	2.49
C_6H_5Cl	5.81	1.42	1.92	2.73
$C_6H_5CH_3$	2.51	0.86	2.14	1.48
C_6H_5OH	32.10	0.76	5.98	11.95
C_5H_5N	2.33	1.95	1.49	1.65
$C_{10}H_8$	87.70×10^3	19.71	—	4.39×10^4

E. GENERAL DISCUSSION

The above survey is not complete; for example, it does not include suggestions, frequently made (160, 285–287), that all free radicals are electrophilic. Other treatments are the electron spin or "residual valency" concept of Moffitt (234), which is related to the ideas of free valence and valence libre, and the "frontier electron" method of Fukui (118, 119, 138), which attempts to treat all forms of substitution by consideration of the densities of the frontier electrons present in the isolated molecule.

Reference to the above sections shows that the methods which are capable of a more than qualitative picture are based on the molecular orbital (M.O.) treatment. Although there is abundant evidence that these M.O. approximations (for the M.O. method is inherently an approximation) are consistent when applied to cyclic alternant hydrocarbon systems, it cannot be assumed that the same result will be obtained when they are applied to ionized systems, free radicals, or heteromolecules (41, 72).

Of the treatments available, the one most likely to be a reliable guide is Wheland's atom localization theory. Dewar (98, 100–105) believes this method to be the only valid one. The assumptions made about the transition state are reasonable, and the results, for any of the three forms of substitution, may be expressed directly in terms of an observable quantity: namely, the energy of activation. The method has been used very successfully by Brown (34–40) in attempts to predict the results of Diels–Alder and similar reactions.

Unfortunately, whenever heteromolecules are treated, whatever the theory employed (48, 290), certain parameters must be introduced into the mathematics. The choice of values for these is somewhat arbitrary, though in some cases rough figures are available (48), and in others attempts have been made to obtain the relevant experimental data (216–221). Since the number of parameters is usually three, then by suitable choice of values, the two types of substitution, heterolytic and homolytic, may be qualitatively described. For quantitative prediction, accurate values for the parameters are essential and the importance of possessing such data cannot be overemphasized. It is to be noted that the parameters used in the calculations for chlorobenzene (290) (table 6) had to be very carefully chosen in order to explain the ortho–para-directing, but deactivating, effect of the chlorine atom in electrophilic substitution (*cf.* table 1). The case of naphthalene is very important, for the predictions of the two methods (tables 5 and 7), each based on calculations which do not involve the use of arbitrary parameters, do not agree. Thus, free valence predicts a much lower reactivity than the method of Wheland. The reason for this may be that the partial fixation of the bonds in naphthalene (246, 259) was neglected, and all the carbon atoms were treated as if they were identical. Alternatively, it may be argued that the high reactivity predicted by the atom localization energy treatment is due to a gross exaggeration by this method of the degree of localization which takes place in the transition state and that a factor should be introduced to allow for this somewhat restricted localization. It is difficult to see, however, why this should affect only calculations on condensed nuclear systems.

The anticipated agreement among some of the theories has been demonstrated in a qualitative sense, although this correspondence does not prove any one of the theories correct. For all the cases considered, small energy differences are involved. Any small errors in the corresponding calculations, caused by neglect of overlap integrals, incorrect parameter values, etc., will be magnified in the evaluation of the reaction rate through the application of the exponential formula (equation 28). The employment of energy differences, however, has some recommendation, for consistent errors are eliminated when the differences are considered.

In all the treatments, particularly for homolytic reactions, the predictions have been made regardless of any other form of possible reaction. For example, the free-radical attack on a molecule could give rise to a heavily stabilized solvent radical, and nuclear substitution would then not take place at all. The figures obtained indicate the nuclear reactivities only and, although perfectly legitimate, are not to be assumed to indicate that the corresponding type of substitution will necessarily be observed.

It must also be pointed out that in none of the methods described above is any account taken of the influence of the reagent on the course of substitution reaction. Thus, for example, identical relative rates are predicted (table 6) for nitration, or chlorination, or, indeed, for any electrophilic substitution of a given compound. However, wide differences exist between the experimentally determined values of these rates (Section II). Since relative rates are under consideration, these differences cannot be due to variation in the *P*-factor (equation 27). This implies that the energies of activation for attack, at the same position r in C_6H_5X, by the entities causing nitration and chlorination, respectively, must be different. In the field of homolytic substitution, too, the relative rates and ratios of isomers have been found (51, 79, 146) to be dependent on the nature of the radical effecting substitution. Thus the introduction of substituents of an electron-attracting character into the para position of the phenyl radical results in the assumption by the radical of a measure of electrophilic character, while an electron-repelling substituent has the opposite effect of conferring upon the radical the properties of a nucleophilic reagent (*cf.* tables 12 and 13 in Section V,E and Section VI,A).

It is perhaps unfortunate that in testing quantitative theories of aromatic substitution attention has been directed largely to heterolytic reactions, since the homolytic reactions, being free from strong "Coulombic" effects, are probably more amenable to quantitative treatment. For homolytic substitution it is seen that all the treatments are in agreement in predicting that substitution by a neutral free radical into the nucleus of C_6H_5X (where there is no restriction on the group X within the previous relevant discussion) will be somewhat faster than the corresponding substitution in benzene, and that the activation is greatest in the ortho and para positions. In the following sections the recent experimental data are discussed in the light of these predictions, which could have been made largely before these data became available.

V. COMPETITIVE REACTIONS

A. THE COMPETITIVE METHOD

Relative rates of homolytic substitution are best determined by the competitive method, and a number of such determinations have been reported recently. The idea embodied in the use of the competitive technique (197) is to allow two molecular species to compete with each other for reaction with a grossly insufficient quantity of the reagent, and to determine the relative amounts of product formed from each compound. From this, the ratio of total reaction rates for the two compounds may be calculated (see Sections II and IV,B).

In order that the application and validity of the technique may be appreciated, it is necessary to consider the following points:

1. The foregoing evidence (Section III) shows that it may be assumed that in homolytic bimolecular aromatic substitution the substitution is effected by first-order attack of the phenyl radical upon the aromatic solvent molecule. The actual kinetics of this substitution step cannot be directly studied (5, 286), since in all the above D, G, H, and P reactions (Section III) this is not the observable rate-determining step. Thus, for example, in the H reaction the rate-determining stage is the intramolecular rearrangement (equation 11). The complicating circumstances of the production of the radical by preliminary change, either slow or reversible, or simultaneous interaction with other substances in mutually independent side reactions can be overcome by the competitive method. The essential requirement, which is satisfied, is that the attack of the active entity upon each of the two solvents should be of the same kinetic order (*cf.* Wegscheider's test for simultaneous reactions of the same order).

2. The reaction employed in the competitive experiments must be homogeneous, for otherwise physical or mechanical differentiation, e.g., the relative solubilities of the organic compounds in the phase where reaction takes place, may become important. This implies that the Gomberg reaction cannot be used and renders less reliable the only early experimental work available. This work is that of Hey (141), who found that nitrobenzene was approximately four times more reactive than toluene in phenylation.

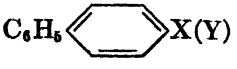
3. The decomposition of benzoyl peroxide (Section III,B) is the most useful reaction for competitive experiments, since the simple phenyl radical is ultimately produced, the reaction medium is homogeneous, the peroxide can be obtained in a good state of purity, and the reaction product is relatively clean. In the reaction mixture using the two solvents C_6H_5X and C_6H_5Y, the benzoyloxy, phenyl, and possibly solvent radicals can be expected to form some or all of the compounds shown in Chart I by successive substitution reactions:

Chart I: Some possible products from competitive reaction

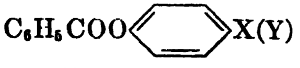
(*a*) *Simple products:*

C_6H_6	C_6H_5COOH
Benzene	Benzoic acid
(usually negligible; *cf.* Section III)	

(*b*) *Monosubstitution products:*



X(or Y)-Biphenyls

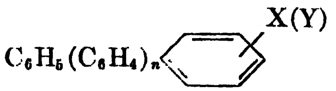


X(or Y)-Phenyl benzoates

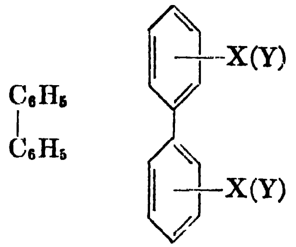
$C_6H_5C_6H_4COOH$

Biphenylcarboxylic acids

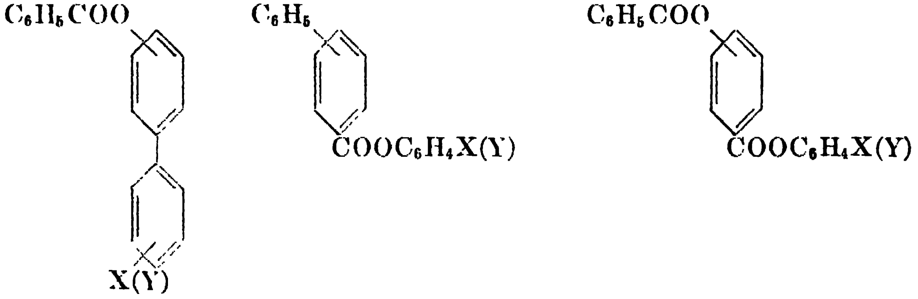
(*c*) *Polysubstitution products:*



X (or Y)-Polyphenyls



Dimerization products (usually negligible; *cf.* Section III)



Substituted esters

From a mixture of reaction products derived from the initially equimolecular mixture of solvents, the ratio of the weights of the monophenylated solvents, i.e., the ratio of X-biphenyl to Y-biphenyl, has to be obtained. This molecular ratio is not directly the ratio of the reaction velocities of the respective total substitutions, since the molar composition of the solution has changed during the course of the reaction. By using a large excess of mixed solvent, however, this error is minimized and the product ratio gives ${}^{X}_{Y}K$ directly.

The formation of large quantities of polysubstitution products like those shown under (c) above must be avoided, as differential removal of any one of the products of monophenylation may invalidate the value of ${}^{X}_{Y}K$ obtained. The dilution mentioned in the previous paragraph tends to minimize this occurrence but, if such highly substituted products are found in the product, their quantities must be determined and any necessary corrections applied. In the past, polysubstitution has been observed in many (1, 5, 169) free-radical reactions with the isolation of quaterphenyl and similar compounds. This was thought to be the reason for the production of large quantities of tar in these reactions and the low

TABLE 8

A. Relative rates of phenylation of compounds C_6H_5X

X	(1) P Reaction 80°C.	(2) P Reaction 70°C.	(3) H Reaction 20°C.	X	(1) P Reaction 80°C.	(2) P Reaction 70°C.	(3) H Reaction 20°C.
NO_2	4.0		3.0	i-C_3H_7†	0.87		
F	1.35			t-C_4H_9	0.87		
Cl*	1.44	1.35	1.5	C_6H_5	4.0		3.0
Br	1.75	1.35	1.6	CH_3O	2.5	1.2‡	2.0
I	1 80	1.65		SO_2CH_3		1.5	
CN		3.7		CF_3		0.99‡	
CH_3†	1.68		1.9	$Si(CH_3)_3$		1.06‡	
C_2H_5†	1.24						

* Approximate value (97) for ${}^{Cl}_{H}K \backsim 2.0$.

† Corrected for side-chain attack (*cf.* Section V,B,7).

‡ Data of Rondestvedt and Blanchard (251).

B. Relative rates of phenylation of miscellaneous compounds

Compound	(1) P Reaction 80°C.	(2) P Reaction 70°C.	(3) H Reaction 20°C	Compound	(1) P Reaction 80°C.	(2) P Reaction 80°C.	(3) H Reaction 20°C.
Pyridine	1.04	1.5	1.0	p-Di-*tert*-butylbenzene	0.63		
Naphthalene	24		20	p-Dichlorobenzene	2.69		
p-Xylene	3.29†		2.7	s-Trichlorobenzene	5.02		
lene	6.17†		6.7				

† See equation 56.

yields of biaryl obtained. The presence of such high-boiling residues has been typical of these reactions (Section III, D).

B. EXPERIMENTAL RESULTS AND DISCUSSION

1. The results of competitive reactions, using phenyl radicals, are shown in tables 8A and 8B.

The results obtained by Hey and his coworkers (1–6, 49–51, 161, 167, 168) are given in column (1). Two reference solvents, nitrobenzene and pyridine, were used and, in many cases, different indirect determinations of the relative rates by the method described in Section IV,B,6 (equation 33) served to check the values obtained and to demonstrate that the results obtained with solvent pairs in which one component was pyridine were not affected by complicating phenomena, e.g., solvent complexing (81). The benzoyl peroxide was allowed to decompose in dilute solution (6 g. per 200 g. of mixed solvent; mole fraction 0.01) at 80°C. for 72 hr. Procedures and analyses were independently checked as to their quantitative accuracy. The products isolated and identified generally accounted for about 85 per cent of the peroxide used.

Column (2) contains the results obtained by Dannley, Gregg, Phelps, and Coleman (80, 81) and by Rondestvedt and Blanchard (251), based on the use of pyridine as reference solvent and with rather higher peroxide concentrations (mole fraction 0.03–0.06) than those employed by Hey et al.

The results obtained by Huisgen and Sorge (186, 192), who employed the H and not the P reaction and who used pyridine as reference compound, are given in column (3).

2. The final reaction mixture for all column (1) experiments in which nitrobenzene was present as solvent was always dark-colored. This was never observed in any other case, e.g., using benzene and/or chlorobenzene as solvent, and indicates that reduction of the nitro group has taken place with further interaction of these reaction products with the peroxide to give colored nitrogen-containing compounds.

3. In certain column (1) reactions high-boiling residues were obtained in quantities approaching 50 per cent of the yield of biaryls (2, 5). These were identified as mixtures of terphenyls and quaterphenyls. Residues were not obtained in reactions in which one component of the mixture was nitrobenzene, except for the reactions with mixtures of nitrobenzene with anisole and naphthalene (1). Apart from these exceptions, which are considered separately below, it appears that polyphenylation products are produced only in the absence of a "fast" solvent, such as nitrobenzene (1, 50) (${}^{\mathrm{NO}_2}_{\mathrm{H}}K = 4$). Moreover, in Dannley's work (80, 81) high-boiling residues were always encountered when "slow" solvents were used. In the one case where a "fast" solvent was employed (C_6H_5CN), only a small residue was obtained. The explanation of this is probably that in the presence only of relatively unreactive solvents (${}^{\mathrm{X}}_{\mathrm{H}}K \sim 1$), a phenyl radical collides with a sufficient number of molecules for there to be a fairly large probability of its eventual reaction with an already phenylated molecule, since, although such molecules are present only in low concentration, their reactivity is considerably greater than that of the solvents (*cf.* the relative rate for biphenyl itself, ${}^{\mathrm{C_6H_5}}_{\mathrm{H}}K = 4.0$). However, in the presence of a "fast" solvent such as nitrobenzene, whose reactivity is equal to that of biphenyl, the probability of reaction of the phenyl radical with an already phenylated molecule is very much reduced. The nonoccurrence of polyphenylation products in the phenylation of biphenyl (49) (*cf.* Section V,B) further demonstrates that prohibition of polysubstitution is not confined to nitrobenzene but is dependent only on the relative rate of phenylation of the solvent. On this basis, the occurrence of a high-boiling resin in the product of the reaction with a mixture of pyridine and mesitylene (1) appears anomalous, since mesitylene is a "fast" solvent. Other considerations are relevant in this instance, however, which are considered below (Sections V,B,7 and V,B,8). However, simple polysubstitution is not a complete explanation of the formation of compounds of high molecular weight, as has been shown by Dannley (81), who isolated a very small quantity of a basic bromine-containing substance from a mixture of C_6H_5Br and C_5H_5N. This could be explained by the generation of small quantities of solvent radicals, a possibility which has already been discussed (Section III).

4. In those cases where resins are obtained, corrections should be made to allow for the possible differential removal of biphenyl-type products by further substitution (see Section V,B,3). This could be done in two ways: firstly, by accurate isolation and analysis of such residues to estimate the weights of the respective

biphenyls affected; and secondly, by measuring the ratio in which the biphenyls are removed from a solution by phenylation.

The first method was used in the determination of the figures in column (1) of table 8. It was found (1, 5) that, to a first-order approximation, the X- and Y-biphenyls were removed by further phenylation in that ratio in which they were formed by phenylation of C_6H_5X and C_6H_5Y, i.e.:

$${}^{X}_{Y}K \sim {}^{XC_6H_4}_{YC_6H_4}K \tag{52}$$

If this were rigorously correct, then no correction need be applied to the value of ${}^{X}_{Y}K$ to allow for polysubstitution effects. Dannley made no correction to the column (2) figures for the selective removal of these compounds. It is, however, shown in Section VII,B,2 that this effect is present and that corrections are therefore necessary. The near equality for equation 52 which is observed in many cases is explained by the fact that resins are obtained only in mixtures of low reactivity, e.g., C_6H_6 and C_6H_5Cl, where the directing groups X and Y are of similar power (table 8).

However, from the point of view of the competitive experiments it is most desirable to keep polysubstitution to a minimum by the use of dilute solutions.

5. In general, the amount of benzoic acid formed in reactions with benzoyl peroxide corresponds roughly to one mole of benzoic acid per mole of peroxide (see table 9).

This is consistent with the simplest possible stoichiometric picture of the reaction. However, in certain cases such a simple picture is obviously not sufficient to explain the facts. The most notable of these exceptions is the case of naphthalene. In the competitive experiment in which benzoyl peroxide was decomposed in an equimolar mixture of nitrobenzene and naphthalene, and in decompositions of benzoyl peroxide in naphthalene alone (1), considerably more benzoic acid was formed after hydrolysis of esters than is required by the stoichi-

TABLE 9

Benzoic acid isolated from competitive reaction mixtures, using 6 g. of benzoyl peroxide

Aromatic Compound	C_6H_6	C_6H_5F	C_6H_5Cl	C_6H_5Br	C_6H_5I	$C_6H_5NO_2$	p-$C_6H_4Cl_2$	Table 8 reference
*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	
$C_6H_5NO_2$	3.0	2.60	2.8	2 8	3.5	—	2 7	Column (1)†
C_5H_5N	3.3	—	3.2			3.3		
C_5H_5N	3.6		3.9	4.2	3.9			Column (2)‡
	s-$C_6H_3Cl_3$	$C_6H_5CH_3$	p-$C_6H_4(CH_3)_2$	s-$C_6H_4(CH_3)_2$	$C_6H_5C_6H_5$	$C_6H_5OCH_3$	$C_{10}H_8$	
	grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	
$C_6H_5NO_2$	2.3	3.1	3.6	3.6	2 8	4.9	5 2	Column (1)†
C_5H_5N								
C_5H_5N								Column (2)‡

* Reference solvents used in competitive reaction.

† 80°C.; figures include free acid and acid resulting from the hydrolysis of esters (see chart 1 on page 156)

‡ 70°C.; only free acids included, containing about 7 per cent of phenylbenzoic acids.

ometry of the simple phenylation reaction. However, the excess of benzoic acid is accounted for by the acid present as 1- and 2-naphthyl benzoates, since a sufficient quantity of mixed naphthols was isolated after hydrolysis. Thus it appears that the very reactive solvent, naphthalene, is susceptible to attack by $C_6H_5COO\cdot$ radicals (benzoyloxylation) which, though less active homolytic reagents than phenyl radicals, are probably present in higher concentration (*cf.* Section III,B,2). Again, a larger amount of benzoic acid is produced when pyridine is used as the reference solvent. This was thought (80, 81) to be due to the formation of reactive complexes between pyridine and benzoic acid or other substances present in the mixture. Variation in the quantity of phenylbenzoic acids isolated with different solvent pairs was also attributed to this complexing action but is, however, capable of simpler explanation. The amount of these compounds formed depends upon the reactivity of benzoic acid relative to that of the other substances present. From table 12, benzoic acid might be expected to have a rate value of ${}^{\mathrm{COOH}}_{\mathrm{H}}K \sim 3.7$, and it follows, therefore, that in mixtures of solvents of low reactivity large amounts of phenylbenzoic acids will be formed. The problem is complicated with these mixtures, however, by the formation of high-boiling residues (Section V,B,3 and V,B,4).

Anisole is exceptional, for it gives rise to mutually untenable conclusions. According to table 9 and the foregoing, anisole should be a very reactive molecule, and this is contrary to the ${}^{\mathrm{X}}_{\mathrm{H}}K$ rate data of table 8. This is discussed further below (Section V,B,8).

6. The halogen series of relative rates (2)

$$\begin{array}{lcccc} X = & F & Cl & Br & I \\ {}^{X}_{H}K = & 1.35 & 1.44 & 1.75 & 1.80 \end{array} \tag{53}$$

illustrates the effect of moving down a group of the Periodic Table. Though the differences are small, the values have been obtained by cross-checked experiments and are confirmed by the various groups of workers. It would have been unwise to place complete reliance in the data, however, until the fluctuation in the amount of acid and resin obtained in each case had been explained and shown to have no effect on the ${}^{\mathrm{X}}_{\mathrm{H}}K$ value (see Sections V,B,5, V,B,7, and V,B,8). This series should be compared with the values predicted (tables 5 and 17) and related to the discussion in Section IV,C,5,(iii).

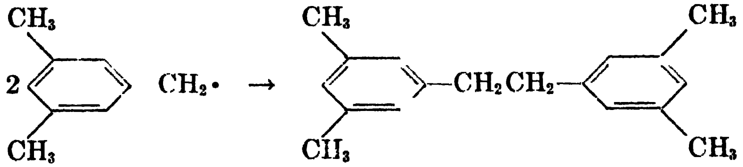
7. The methylbenzenes (1) are extremely interesting. The progressive introduction of methyl groups gives:

$$\begin{array}{lccc} X = & CH_3 & p\text{-}(CH_3)_2 & s\text{-}(CH_3)_3 \\ {}^{H}_{X}K = & 1.85 & 3.29 & 6.17 \end{array} \tag{54}$$

but the situation is not clear-cut.

With nitrobenzene as the reference solvent it was found that nitro group analyses on the biphenyl fraction did not agree with those for elementary nitrogen from combustion analyses. This was attributed to the presence of already reduced nitrogen compounds not estimated by the former method, and this postulate was substantiated when a very small quantity of basic material was isolated from the $s\text{-}(CH_3)_3C_6H_3/C_6H_5NO_2$ product-mixtures.

Investigation (1, 3) of the composition of the neutral reaction products resulting from the $p\text{-}(CH_3)_2C_6H_4/C_5H_5N$ and $s\text{-}(CH_3)_3C_6H_3/C_5H_5N$ reactions showed that they consisted of biphenyl fraction and resin. (From Section V,B,3 above, this resin should not have been formed, since ${}^{s\text{-}(CH_3)_3}_{\;H}K > 4.0$; the explanation will become apparent in what follows.) The biphenyl fraction was observed to solidify partially and the crystals which formed were removed and identified as the dimers of the corresponding methyl-substituted benzyl radicals. Thus, for example, in the case of mesitylene the corresponding radical is stabilized by resonance, and the dimer 3,5,3′,5′-tetramethyldibenzyl results:



(55)

The presence of this radical is the probable cause of resin formation in these compounds.

These results were the first to show side-chain attack by aryl radicals. The weights of the substances involved in the above cases allow the calculation of the percentages of side-chain attack to total attack. These figures are inherently approximate, owing to the experimental work and the assumptions which have to be made. Thus it has to be assumed that the substitution and hydrogen abstraction are effected by the same radical, i.e., free phenyl. This is somewhat justified, since the quantity of benzoic acid obtained from these experiments is normal. Moreover, mesitylene is known to behave as a typical aromatic molecule in peroxide decomposition, i.e., there is no induced decomposition of peroxide by the benzyl-type radical (see Section III,B and Section V,B,8). Furthermore, it is reasonably assumed that this dimerization also occurs in the competitive experiments using nitrobenzene as reference. Correction to the apparent relative rate values (equation 54) for the occurrence of side-chain attack gives the following figures:

$$\begin{array}{lllll} X & = CH_3 & p\text{-}(CH_3)_2 & s\text{-}(CH_3)_3 \\ {}^{X}_{H}K & = 1.68 & 0.23 & 4.2 \end{array} \qquad (56)$$

Thus, for the first time, a group X has been found which deactivates the nucleus for radical phenylation. Further work has since shown that *tert*-butylbenzene, *p*-di-*tert*-butylbenzene, and isopropylbenzene (50, 168) emulate this behavior. Explanations for both this order, assuming it to be a true one, and the effects observed with *tert*-butylbenzene and isopropylbenzene are given later (Sections VII,A,4 and VII,B,2).

Dannley and Zaremsky (83, 84) have confirmed the existence of simultaneous side-chain and nuclear reactions by using mixtures of a single solvent and peroxide. It is reported that both ethylbenzene and isopropylbenzene give

TABLE 10

Side-chain attack in the reaction of alkylbenzenes with benzoyl peroxide

Alkylbenzene	Dannley and Zaremsky (83, 84)	Rondestvedt and Blanchard (250)	Hey, Pengilly, and Williams (167, 168)
	per cent by weight	*per cent by weight*	*per cent by weight*
Toluene .	—	$\not>15$	13
Ethylbenzene .	67	—	55
Isopropylbenzene.	33	59	60.5

stabilized benzyl-type radicals which dimerize, but that toluene undergoes a unique reaction to form a very small quantity of diphenylmethane. This result has been disproved by the more recent work of Rondestvedt and Blanchard (250) and of Hey, Pengilly, and Williams (167, 168). Both groups of workers agree that no diphenylmethane is formed, but that a small quantity of bibenzyl (ca. 10 per cent) results from dimerization of benzyl radicals. In addition, all these groups of workers have measured the amount of side-chain attack which takes place in the phenylation of ethylbenzene and isopropylbenzene, resulting in the formation, respectively, of *dl*- and *meso*-2,3-diphenylbutane (in equal amounts) and 2,3-dimethyl-2,3-diphenylbutane (dicumyl). The results obtained for the relative amounts of side-chain and nuclear attack on these hydrocarbons are given in table 10. In addition, Rondestvedt and Blanchard measured the relative amounts of the products of side-chain and nuclear attack on toluene and isopropylbenzene by phenyl radicals derived from *N*-nitrosoacetanilide and 3,3-dimethyl-1-phenyltriazene. Substantially the same results were obtained with these sources, except in one case—the decomposition of *N*-nitrosoacetanilide in toluene—in which the temperature was maintained below 25°C. throughout. In this experiment no side-chain attack was observed.

It is seen from table 10 that, as might have been predicted, the substitution of methyl groups at the α-carbon atom of the side chain renders hydrogen atoms attached to this atom more susceptible to removal by homolytic attack.

8. In the preceding discussion certain solvents have appeared to give rise to anomalous reaction products. The observations are difficult to explain and the possible suggestions conflicting. Table 11 presents the facts. The columns indicate in order the values of the total relative rate ($K_{\text{calc.}}$) predicted by the mathematical theoretical treatments (Section IV) and the observed ($K_{\text{obs.}}$) values of the free-radical reactivity for nuclear phenylation, the production of resins with the solvent mixtures using reference solvents $C_6H_5NO_2$, C_6H_6, and C_5H_5N, whether or not induced decomposition is shown in the P reaction (Section III,B), and the quantity of benzoic acid which is recovered from the products. Phenol is included in the table as it is important in the discussion (see 300, 301).

In Section V,B,5 above, the acid-recovery figures were discussed, and it was pointed out that a high reactivity of the molecule in allowing benzoyloxylation would give rise to a large amount of benzoic acid. Thus, the total recovery of acid from the reaction with phenol (table 11) could be explained by the very high solvent reactivity, $K_{\text{calc.}}$, facilitating benzoyloxylation and inhibiting

TABLE 11

Anomalous behavior in reactions with benzoyl peroxide

Aromatic Compound	$K_{calc.}$ (Table 7)	$K_{obs.}$ (Table 8)	Resin† in Solution with		P Reaction; Induced Decomposition‡ (Section III,B)	C_6H_5COOH‡ (Table 9)
			$C_6H_5NO_2$ (Sections V,B,3 and V,B,4)	C_6H_6, C_5H_5N (Sections V,B,3 and V,B,4)		
C_6H_5OH	11.95		?	?	++	++
C_6H_5Hal	2.7		n(?)	+	n	−
$C_6H_5OCH_3$			+	?	n	+
s-$(CH_3)_3C_6H_3$			n(?)	+	n	n(+)
$C_{10}H_8$			+	?	?	+

* See Sections VII,B,2 and V,B,7, equations 54 and 56

† n denotes normal behavior, i e , no resin, normal acid production, and very small induced rate of peroxide decomposition.

+ denotes increased behavior or production of correspondingly increased quantity.

− denotes decreased behavior or production of correspondingly decreased quantity

? denotes unknown behavior

decarboxylation of the $C_6H_5COO\cdot$ radicals. This, however, neglects the fact that phenol does not behave as a typical aromatic solvent in the P reaction.[5] Owing to the production of stabilized aryloxy radicals (12, 65, 66, 235, 236) a very high rate of induced decomposition is exhibited. The presence of such solvent radicals is proved by the isolation of the corresponding dimerization products in certain instances (65, 66). These radicals possess a high specific activity in promoting the chain decomposition of the peroxide (steps (b) and (c), scheme IV, equation 24, are very fast). Thus, here the $K_{calc.}$ value is misleading; some other reaction takes precedence over nuclear substitution (see Section IV,E).

Anisole, in distinction to phenol, does not show induced decomposition (235, 236). It does, however, produce resin and show high acid recovery in competitive reactions with nitrobenzene (1). It is suggested that an alkyl hydrogen atom is removed by $C_6H_5COO\cdot$, to give the acid and the stabilized aryloxy-alkyl radical $C_6H_5OCH_2\cdot$. It must be assumed that this radical does not promote induced decomposition of the peroxide, but does contribute to the formation of high-molecular-weight compounds. To some degree, the occurrence of resins when mesitylene is used in these experiments supports this viewpoint (Section V,B,7).

It is impossible, as yet, to suggest the reason for the occurrence of the resin with the $C_{10}H_8/C_6H_5NO_2$ mixture (1). Using the former solvent alone in the P reaction, the resin has been shown to consist mainly of unidentified hydrocarbons. This suggests the formation of solvent radicals but is opposed to the known fact that this solvent has a high free-radical substitution reactivity, as evidenced by $K_{obs.}$ and the fact that extensive benzoyloxylation occurs (79, 249).

C. THE PRESENCE OF ACTIVE HYDROGEN

Previous discussion (Sections III and V) has indicated that hydrogen atoms, or other labile forms of hydrogen, may be formed in homolytic arylation. Much controversy has centered around this point (287, 288) and it is necessary to clarify the issue. The fact that molecular hydrogen was not evolved in the P reaction (78) gave some support to the solvent-radical decomposition mechanism (scheme II, equation 20), though this should have been rejected for other reasons (see Section III,B). The absence of hydrogen, however, does not preclude the presence of free hydrogen atoms which, being very reactive, would never be able to dimerize.

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[5] See references 300 and 301.

Confirmation for the existence of hydrogen atoms arises from the following:

(i) The negative argument (Section III) based on the fact that no appreciable quantities of solvent radicals are formed in these reactions, the ratio of hydrogen-atom ejection to solvent-radical formation being about 120:1 (190) (equation 12).

(ii) The isolation of quantities of quinhydrone from some of the typical free-radical reactions (Section III) when quinone was present in the mixture (59, 190, 293–298).

(iii) The qualitative observation from competitive and preparative experiments (see Section V,B,2) that whenever nitrobenzene was used in the P reaction a very dark-colored reaction mixture was obtained, whereas relatively colorless products were obtained from a nitrogen-free solution, e.g., chlorobenzene or a C_6H_6/C_6H_5Cl mixture (1). This is attributed to reduction of the nitro group.

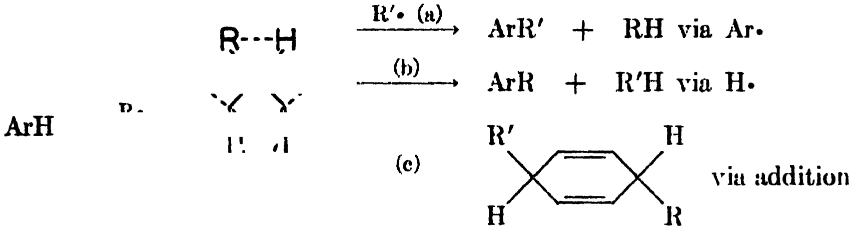
(iv) Using the decomposition of benzoyl peroxide, with both nitrobenzene alone and the competitive mixture alkylbenzene/$C_6H_5NO_2$, the production of primary amine was suspected (see Section V,B,6). Furthermore, in a similar competitive experiment with $C_{10}H_8/C_6H_5NO_2$, aniline has been identified (1, 5).

Of these facts the last is vitally important, since it immediately aids the rejection of reaction scheme II (Section III). Moreover, reference to the proposed mechanism (scheme III, equation 21) and the relevant discussion indicates why the amine was found in reasonable quantity in this mixture and not in any other case (190, 192). In the normal situation, the most efficient acceptor of hydrogen atoms present in the reaction mixture is the benzoyloxy radical; hence, normally, the ejected hydrogen atoms appear in the product as benzoic acid. However, naphthalene is an unusually reactive compound and is therefore susceptible to benzoyloxylation. Since this reaction results in the consumption of benzoyloxy radicals with the production of the same number of hydrogen atoms, the nitrobenzene present in the mixture must be called into play as an oxidizing agent or acceptor for the excess of hydrogen atoms. This must result in an increased production of the products of reduction of nitrobenzene.

D. THE SUBSTITUTION STEP

The "RH scheme" of Gelissen and Hermans (122–129) (Section III,B; equation 13) was the first clear attempt to explain the substitution step in the arylation of aromatic solvents with acyl peroxides. The same scheme was advocated subsequently by other workers (26, 112, 297, 298). More recently, Huisgen and Horeld (190) and Huisgen and Sorge (192) have advanced the so-called "kryptoradical" theory, in which the radicals are never actually free but in which the dissociation of the radical source and the attack on the aromatic compound are synchronous processes. Such a scheme is akin to the RH scheme, which envisaged the formation of solvent–acyl peroxide complexes. In an attempt to establish the degree of "freedom" of aryl radicals the losses of configuration have been measured when optically active 2-methyl-6-nitrodiphenyl-2′-carboxylic acid peroxide and the diazohydroxide derived from nitro-2′-aminodiphenyl were decomposed in benzene (184). Since some racemization and some retention of configuration occurred, a mixed mechanism was indicated in this case.

Other theories have considered the activated complex in the reaction to be formed between the radical itself and the solvent (20, 24, 251). For phenylation, it is obvious that the phenyl radical is the prime mover in the reaction (Section III,C), but it has to be decided whether the hydrogen atom is removed synchronously with the attachment of the phenyl group, or in a fast reaction, which is not of kinetic significance, subsequent to the addition of the phenyl radical. In developing the suggestions made by some workers (285, 289) it is proposed that the attack of R• on ArH results in the formation of an intermediate R—Ȧr—H. By assuming stability of the quinonoid forms, this intermediate might be expected to possess increased free valence at positions ortho and para to the group R. (An additional effect may be produced by the exaltation of the homolytic substitution reactivities of these sites, owing to the presence of the R group and the small amount of conjugation it possesses with the nucleus.) On approach of a second radical R′•, three overall results are possible (equation 57):



(57)

The R—Ȧr—H intermediate may be thought of as a π-complex (289) or as a σ-complex in the formation of which a π-complex is intermediate (251). Significant evidence is available to show that this complex formation takes place in reactions involving radicals other than phenyl, and that the reaction does take place in two stages. Hence, when ArH = anthracene, a compound of type (c) can be obtained where R = 2-cyano-2-propyl- (20), Cl (26) and R′ = ArRH, i.e., the *p*-quinonoid form possessing free valences at the 9,10-positions is very stable. This type of reaction for anthracene is well known, e.g., keto–enol tautomerism, addition reactions, bromination, etc., and is expected, since the two side rings may take up the benzenoid form. Theoretically, the 9,10 para localization energy has been shown (34–40) to be small. When simple aromatic solvents, C_6H_5X, and hydroxyl radicals are employed, the favored reactions are (a) and (c), and we have seen that aryl radicals react via (b). This behavior can be explained by a consideration of the stabilities of the solvent radicals it is possible to form and the strengths of the bonds involved.

Szwarc has shown (199, 271–274, 277) by a study of the bond-dissociation energies involved, that although the biphenyl-coupling resonance energy is gained in the phenylation reaction (b) (additional energy amounting to 14–25 kcal. relative to CH_3CH_3 is obtained), this is still not sufficient to explain the substitution. Szwarc postulated a hot-complex $C_6H_5—\dot{A}r—H$ (*cf.* the intermediate in equation 7) with (π–π) electron interaction in the C_6H_5–Ar "bond" and another radical taking off the hydrogen atom. It is difficult to explain the nuclear arylation of toluene, rather than exclusive side-chain attack (a) (equation 57; *cf.* Section V,B,7), without invoking the presence of this second radical. It is significant that, in most substitution reactions with benzoyl peroxide, the yield of benzoic acid accounts for half of the original peroxide (table 9). This implies a pseudo-termolecular collision, wherein the phenyl radical effects substitution and the "liberated" hydrogen atom combines with the $C_6H_5COO\cdot$ radical remaining (see Section II,B). Returning to reaction scheme III (Section III,B), which describes the observed kinetic and preparative work, it is seen that this process is the one described. If the solvent readily induces substitution (e.g., naphthalene) and sufficient hydrogen-atom acceptors in the form of radicals $R'\cdot$ (equation 57), and in particular $C_6H_5COO\cdot$, are not available, then the solvent may take up this role with the production of reduced compounds in the mixture (Section V,C). Whether or not the "liberated" hydrogen atom is ever free, as such, it is impossible to say (*cf.* the "kryptoradical" theory (192)). Stockmayer and Peebles (268), Bickel and Kooyman (20), and Boozer and Hammond (24) have concluded that the formation of a radical–solvent complex, associated with a small activation energy, takes place. This formation of the complex must, in any case, be the slow stage in the substitution reaction, since Sheppard (258) has shown that there is no isotope effect when tritiated benzene is allowed to react with benzoyl peroxide and triphenylmethyl. This indicates that the removal of hydrogen from the complex is a fast stage, to which no kinetic significance may be attached, and that, therefore, the activated process must be the formation of the complex.

The favored reaction of the methyl radical would be expected to be that of hydrogen-atom abstraction (a) with the formation of methane (276, 280). This is observed (275) with aliphatic-type solvents but not with benzene or pyridine (131, 275, 276, 280). Here the main reaction appears (275) to be substitution (b) with some double addition to form unsaturated compounds of type (c), but these have not been isolated. The methyl radical has been reported not to attack the side chain of toluene (*cf.* Section V,B,7; 275). These results point to the fact that the addition complex for this reaction may have some stability and therefore a finite life in solution, so that addition of a further radical can take place. If the activating group were of stronger power, e.g., as in nitrobenzene (115), then direct substitution by the first methyl radical would be facilitated.

On the other hand, if the attacking radical, instead of methyl were more nucleophilic, e.g., •OH, then hydrogen abstraction would be favored. The reaction of polycyclic hydrocarbons and certain other aromatic compounds with methyl radicals has recently been studied by Levy and Szwarc (211), and their results have been discussed by Hey and Williams (177) and by Coulson (71). These results are further discussed in Section V,E.

Mayo (229) has indicated that solvent–radical complexes may be formed between a styrene polymer molecule and bromobenzene. This is not relevant to the case under review, for the benzyl-type radical of the polymer is able to resonate among various forms (*cf.* equation 55) and will possess a smoothed free valence over the whole molecule. This radical might, therefore, be expected to form a loose *p*-π complex with aromatic molecules, e.g., bromobenzene. With a more highly reactive solvent, e.g., *m*-dinitrobenzene, the polymer radical may be induced to react, and such a solvent should show a moderately good inhibition effect, as observed (139).

The evidence must be carefully assessed before any concrete conclusion can be arrived at concerning the nature of the substitution stage in the phenylation of an aromatic molecule. By analogy with nitration (230), where the addition mechanism is known to occur, and acceptance of gradation between radical and solvent natures and interactions (see Section VI,D), it may be said that the substitution is most probably effected by the addition process. This is consistent with the lack of a kinetic isotope effect. Within this statement are included the various possibilities dependent on the extreme properties of the reactants. Thus, with phenyl radicals, phenol reacts via equation 57a, owing to the stability of aryloxy radicals, whilst chlorobenzene acts via equation 57b.

E. OTHER RADICALS

1. *Radicals other than aryl radicals*

Competitive experiments using radicals other than aryl radicals are summarized in table 12

Column (1): Dannley and Gippin (79) used a series of α-X-substituted naph-

TABLE 12

Relative rates of reaction with radicals other than aryl (79, 109, 139, 211)

Aromatic Compound	${}^{X}_{H}K$			
	(1) $C_6H_5COO\bullet$, 70°C.	(2) $CH_3\bullet$, 100°C.	(3) Polystyryl, 100°C.	(4) $CH_3\bullet$, 85°C.
$C_6H_5CH_3$	1.4	19.2	3.6	
$C_6H_5COOCH_3$	3.7	1.6		
$C_6H_5NO_2$	7.0			
$C_6H_5COC_6H_5$				11
$C_6H_5OC_6H_5$				2
$C_6H_5C_6H_5$				5
C_5H_5N	1.7			3
$C_{10}H_8$				22

thalenes in reaction with benzoyl peroxide. Substitution is effected by the benzoyloxy radical and results in the production of 2-, 4-, or 5-substituted naphthalene derivatives. The esters were isolated semiquantitatively and the ratios of the hetero- and homonuclear substituted compounds were determined. This was assumed to represent the activation of one half of the molecule relative to the other, i.e., ${}^{X}_{H}K$ is found for benzoyloxylation at 70°C. Owing to the fact that the group X will affect both rings, and that there appears to be some peculiarity of the napthalene molecule itself (*cf.* Sections IV,C and IV,D), these values should be accepted with reserve. It might appear that the $COOCH_3$ group has about half the activating effect of the nitro group, and from table 8 this would result in a relative rate of ${}^{COOCH_3}_{H}K = 2.0$ for phenylation. This value seems to be not unreasonable (*cf.* Section V,B,5).

Column (2): These figures were obtained (109) using methyl radicals from diacetyl peroxide. Owing to the fact that free methyl will tend to abstract a hydrogen atom rather than effect substitution, the high rate for toluene is reasonable, since free benzyl radicals are formed.

Column (3): Polymerization work using styrene (139) allows the ratio of rates of (chain transfer to solvent)/(chain propagation) to be measured. Nitrobenzene and *m*-dinitrobenzene are known to be good inhibitors and, on the results of table 8, naphthalene or *s*-trichlorobenzene should be as effective (see Section V,C). The efficiency of polynuclear hydrocarbons as inhibitors has been observed (25).

Column (4): Levy and Szwarc (211) have measured the affinities of a number of compounds, particularly polynuclear hydrocarbons, for methyl radicals. Selected results from this work are included in table 12. The compounds investigated which are not included in table 12 are polynuclear hydrocarbons, which gave very high values for the relative rate. In further discussion of these results (177) it has been shown that a high degree of correlation exists between them and the corresponding results for phenylation (*cf.* table 8). In addition, Coulson (71) has shown that for the condensed nuclear hydrocarbons considered (including naphthalene) a straight-line relationship exists between the logarithm of the methyl affinity and the maximum free valence in the molecule. The absolute values of the free valence numbers are also of the correct order of magnitude. A similar straight-line relationship exists with the atom localization energies; here the absolute values are not of the correct order of magnitude but result in the production of reactivities which are much too high, as in the case of naphthalene (Section IV,E). Thus, a similar error seems to be incurred in all calculations of localization energies in condensed nuclear hydrocarbons.

2 Aryl radicals other than phenyl

Recently determined values for relative rates of arylation of a number of compounds C_6H_5X with substituted phenyl radicals are given in table 13. The same techniques were employed in the determination of these relative rates as were employed by Augood, Hey, and Williams (6) in the determination of the figures listed in table 8, and the same comments therefore apply to them.

TABLE 13

Relative rates of arylation with substituted phenyl radicals at 80°C. (6, 51, 146, 167, 168)

Radical	${}^{NO_2}_{H}K$	${}^{Cl}_{H}K$	${}^{CH_3}_{H}K$
p-$NO_2C_6H_4$	0.94	1.17	2.61
p-ClC_6H_4	1.53	1.02	1.32
p-$CH_3OC_6H_4$	2.92	1.56	—
C_6H_5	4.0	1.49	1.68*
p-$CH_3C_6H_4$	5.13	2.05	1.03

* Approximate value.

Some of these results were measured directly, and others obtained by the cyclic procedure outlined previously (Section IV,B,6, equation 33). The results demonstrate clearly the effect on the relative rates of arylation of electron-attracting and electron-repelling substituents in the para positions of the radicals. The groups NO_2, Cl, and CH_3O attract electrons, and the magnitude of the effect varies in the order $NO_2 > Cl > CH_3O$. The methyl group repels electrons. Thus, the first three radicals of table 13 would be expected to possess some measure of electrophilic character, since the withdrawal of electrons by the substituent groups must result in a deficit of electrons at the position which carries the odd electron. It is conventional to regard hydrogen as the zero for effects of electron attraction and repulsion; following the same convention, the phenyl radical is assumed to be neither electrophilic nor nucleophilic. By similar argument it is seen that the *p*-tolyl radical possesses some nucleophilic character, and therefore that the radicals in table 13 are listed in order of decreasing electrophilic power or increasing nucleophilic power.

The nitro group is known to deactivate the aromatic nucleus towards electrophilic substitution, and to activate it towards nucleophilic substitution. It is to be expected, therefore, that the relative rate ${}^{NO_2}_{H}K$ for arylation with an electrophilic radical should be less than its value for phenylation, and similarly that it should be greater for arylation by a nucleophilic radical than for phenylation. The second column of table 13 shows that this prediction is borne out, and that the magnitude of the effect varies in the order predicted from the magnitude of the electron attraction of the groups concerned. Reference to the third column shows that the rate ratio ${}^{Cl}_{H}K$ is dependent on the nature of the attacking radical in a similar manner. (The slightly anomalous value obtained for ${}^{Cl}_{H}K$ with *p*-anisyl radicals is possibly due to experimental inaccuracy.) In the last column, the order of variation of the relative rates is reversed, since the methyl group is an activating substituent for electrophilic substitution and a deactivating substituent for nucleophilic substitution.

It has been shown (Section V,B,7) that in the phenylation of toluene some side-chain attack takes place. This results in the abstraction of a hydrogen atom with the consequent production of bibenzyl. This process is also observed in the arylation of toluene with the radicals under discussion, and the values given in table 13 for the relative rate ${}^{CH_3}_{H}K$ are those obtained after a correction for the side-chain attack has been applied. They refer, therefore, only to attack on the

TABLE 14

Side-chain attack in the arylation of toluene (146)

Radical.	p-$O_2NC_6H_4$	p-ClC_6H_4	C_6H_5	p-$CH_3C_6H_4$
Per cent bibenzyl. . . .	0	10	13*	42

* Approximate value.

nucleus of toluene. The various proportions of side-chain attack which were determined in the evaluation of these corrections are of interest as they, too, reflect the influence of the substituent groups in the radicals. It is clear that with toluene nuclear substitution should be favored by electrophilic radicals, while side-chain attack should be favored by nucleophilic radicals. The relevant data are given in table 14 and clearly demonstrate the influence of the polar character of the radical.

VI. RATIO OF ISOMERS

A. RECENT RESULTS

Only very recently have reliable figures become available for the proportions in which the substituted C_6H_5X isomers are formed in homolytic reactions. Reference to table 3 and the corresponding discussion indicates the situation prior to 1951, when it was accepted that the para isomer was the compound usually produced in greatest quantity in these reactions. At this time the work of Hey and his collaborators (164) showed that the meta isomer, which had rarely been isolated before could, in fact, account for approximately 10 per cent of the isomer mixture in some reactions, and further results followed quickly. All the published data concerning isomer percentages are given in table 4 of the accompanying paper (92).

From these data, only those values obtained in very careful experiments should be considered in quantitative argument. The best figures are, undoubtedly, the ones derived from spectroscopic analysis of complete isomer mixtures, where mechanical separation of the isomers has been minimized, if not eliminated, in the working-up procedure. Unfortunately, in one or two cases, e.g., naphthalene, the relevant information is not available and the quoted figures, possibly inaccurate, have to be used in the evaluation of the partial rate factors. Moreover, those data obtained by use of single solvents are preferred compared with those obtained when the solvent concerned has been used with pyridine in competitive experiments (see Section V,B). The data used in the evaluation of the partial rate factors for phenylation are presented in table 15 (*cf.* table 4 of reference 92).

In the following discussion on isomer ratios in general, two important facts must be borne in mind: (*1*) the effect caused by change of the radical and (*2*) the effect of the temperature at which the reaction is carried out.

B. PHENYLATION: SUBSTITUTION BY PHENYL

Important conclusions have been based upon the fact that similar isomer ratios have been found to be produced by all of the main homolytic reactions (see Section III). Thus the results of the Gomberg reaction at 5°C. have been com-

TABLE 15

Ratios of isomers used in the calculation of partial rate factors for phenylation at 80°C.

Aromatic Compound	Isomer Percentage			Reference (*cf.* Table 4 in reference 92)
	Ortho or α	Meta or β	Para or γ	
$C_6H_5NO_2$	58	10	32	(5, 164)
C_5H_5N*	58	28	14	(80, 81)
C_6H_5F	54.1	30.7	15.2	(4)
C_6H_5Cl	60.3	25.9	13.8	*cf* table 16
C_6H_5Br	49.3	33.3	17.4	(2)
C_6H_5I	51.7	31.6	16.7	(2)
C_6H_5CN*†	60	10	30	(80)
$C_6H_5CH_3$	66.5	19.3	14.2	(168)
$C_6H_5C_2H_5$	53	28	19	(168)
$C_6H_5C_3H_7$-*i*	31	42	27	(168)
$C_6H_5C_4H_9$-*t*	24	49	27	(50)
$C_6H_5C_6H_5$	48.5	23.0	28.5	(49)
$C_{10}H_8$‡	83.4	16.6	—	(192; *cf.* 232)
$C_6H_5SO_2CH_3$*†	53	33	14	(80)
$C_6H_5CF_3$	20	40	40	(82, 251)
$C_6H_5Si(CH_3)_3$	31	45	24	(251)

* Reaction carried out at 70°C.

† Mixture from competitive reaction with pyridine.

‡ Product of H reaction and possibly inaccurate.

pared (5, 161) with, and found equal to, those of the peroxide reaction at 80°C. However, the difference in temperatures at which these reactions have been conducted has been neglected, and such a comparison is unjustified and invalid. Reference to the reported data for chlorobenzene (5) gives the appropriate figures [(a) and (b), table 16] for the two cases under discussion. [Note: This splitting of the published data, formerly considered together (reference 5 and table 4 of reference 92) increases the experimental accuracy in the groups (a) and (b)]. Additional reported work (80, 81) is also tabulated [(c) and (e)].

Employing equation 39, which was developed in Section IV,B,8, the (a) (G. 278°K.) figures are operated upon to ascertain the values that would be expected from this reaction if it could be carried out at 80°C., i.e., (d) in table 16. It is

TABLE 16

Phenylation of chlorobenzene: spectroscopic values

Method	Temperature	Isomer Percentage			Reference
		Ortho	Meta	Para	
	°*K.*				
(a) G	278	64.6	21.7	13.7	(5)
(b) P	353	60.3	25.9	13.8	(5)
(c) P	343	64	23	13	(80)
(d) G(a)	353	59.6	25.2	15.2	Calculated from equation 39
(e) P	343	54	31	15	(81)

(c) From competitive experiment using C_6H_5Cl and $C_6H_5SO_2CH_3$.

(e) From competitive experiment using C_6H_5Cl and C_5H_5N.

seen that the ortho position, having the smallest energy of activation, becomes less important on increase in temperature, as expected from first principles. The agreement between the (d) and (b) figures, one set observed experimentally at 80°C. and the other calculated as described, is extremely good. Thus, due recognition of the temperature effect has improved the observations and strongly substantiates the conclusions reached in Section III,C. It will be noted that in table 15, which gives isomer ratios for 80°C., some determinations at 70°C. are included. It is now apparent that this difference in reaction temperature has only a small effect on the isomer ratios.

When the C_6H_5Cl/C_5H_5N solvent mixture was used in a competitive experiment, it was found (81) [(e), table 16] that the chlorobenzene gave rise to another set of values for the isomer percentages, i.e., other than the mean between (a) and (b) or the further set of values (c). This led to the suggestion that solvent association was responsible for these deviations (*cf.* Section V,B,5); this is now shown to be very unlikely. Firstly, as presented in table 16, the true isomer percentages for 80°C. are given by (b) or (d) and not, as reported, by the mean of (a) and (b). This does not, however, shorten the gap between (c) and (e). Secondly, evidence is now available (2, 81) for the other halogenobenzenes (92, table 4) and it is seen that, whether pyridine is present or not, there are insignificant variations in the isomer ratios obtained. If complexing of the pyridine occurred with chlorobenzene, it might be expected to occur with the other halogenobenzenes, and these figures do not support this view. For benzoic acid the situation is different, as salt formation with pyridine might be expected. This is shown well in table 4 of the accompanying paper (92) (*cf.* Section V,B,5).

The above discussion shows that, if experiments are conducted at the same temperature, then for a given solvent all sources of phenyl radicals give identical mixtures of isomers in the product. This principle has been applied (169) to show that the decomposition of lead tetrabenzoate in nitrobenzene at 125°C. proceeds via a homolytic mechanism to yield phenyl radicals. In addition, isomer percentages have been determined recently (170) for the phenylation of nitrobenzene (at 125°C.) and pyridine (at 105°C.) with phenyl radicals derived from phenyl iodosobenzoate, *N*-nitrosoacetanilide, and phenylazotriphenylmethane. These results are given in table 17. Although the values for the H reaction are admittedly inaccurate, the figures demonstrate clearly the independence of the

TABLE 17

Comparison of radical sources: isomer percentages obtained (170)

Radical Source	Nitrobenzene (125°C.)			Pyridine (105°C.)		
	Ortho	Meta	Para	α	β	γ
$(C_6H_5COO)_2$	56.3	15.7	28.0	54	32	14
$Pb(C_6H_5COO)_4$	55	16	29	52	32.5	15.5
$C_6H_5I(OCOC_6H_5)_2$	57.5	14	28.5	58	28	14
$C_6H_5N(NO)COCH_3$				46	43	11
$C_6H_5N_2C(C_6H_5)_3$*				53	31	16

* Corrected values (see text).

isomer ratio on the source from which the phenyl radicals are derived. In the case of the reaction of phenylazotriphenylmethane with pyridine, different isomer percentages were obtained, and a solid compound was isolated which was shown to be derived from α-phenylpyridine by reaction with triphenylmethyl. This process therefore resulted in the selective removal of α-phenylpyridine from the isomer mixture, and when the measured isomer percentages were corrected for this, a set of values was obtained which corresponded closely with those obtained using the other radical sources.

Finally, in connection with the validity of the determination of the isomer ratio, it is important to establish that the isomers are not selectively removed by further phenylation.

In a competitive reaction mixture the possibility of selective removal of the X- and Y-biphenyls to form resins was shown to be important in the determination of the relative total rate constant ${}^{X}_{Y}K$ (Sections V,B,3 and V,B,4). Moreover, any such differential reaction between the isomers of either X- or Y-biphenyl will produce an incorrect set of isomer percentage values. Dannley (81) has investigated this point in the following way. A mixture of isomeric phenylpyridines was phenylated, and the isomer percentages determined both before and after reaction. Since no observable change was found, the conclusion was drawn that there was no preferential removal of any of the isomers. It will be shown later (Section VII,B,2), that this deduction is untenable and that these experiments were not sensitive enough to detect the change. Although this effect is usually less important than in the case of competitive experiments (Section V,B,2), the most reliable figures are still those which were obtained under conditions (of high dilution) wherein the incidence of polyphenylation is minimized. With only a few exceptions it is these figures which are used in the calculation of partial rate factors (Section VII).

C. ARYLATION: SUBSTITUTION BY ARYL RADICALS OTHER THAN PHENYL

It has been pointed out (Section V,E,2) that when aryl radicals other than phenyl are employed, the course of reaction is profoundly influenced by the electrophilic or nucleophilic character conferred on the radicals by the polar effects of the substituent groups. It is emphasized that the primary effect of a charge at site r in the compound C_6H_5X now becomes that of attracting or repelling that portion of the radical where the odd electron resides, thereby either assisting or inhibiting reaction. The charges are not ultimately responsible for the reaction, as in heterolytic substitution, and the reaction remains a homolytic process.

This effect is well documented in so far as it is illustrated by relative rates of substitution (Section V,E,2), and some data are also available for its influence on isomer ratios. The work of Dannley and Sternfeld (82) on the arylation of benzotrichloride with phenyl, p-nitrophenyl, and p-chlorophenyl radicals (92, table 4) is relevant in this connection. The reaction of p-nitrophenyl radicals with benzotrichloride is influenced by the following: steric hindrance at the ortho positions due to the bulk of the —CCl_3 group; ortho–para substitution according to the homolytic rules (see Sections VII and VIII); and meta reaction according to the electrophilic rules, since —CCl_3 is a meta-directing group. It is seen (92, table 4) that steric hindrance is prominent, as arylation is completely prevented at the ortho sites, and the electrical effect is such that reaction takes place only at the meta position. With phenyl radicals it is seen that there is a greater steric effect with the —CCl_3 group than with the —CF_3 group, as would be expected. (This steric effect is also illustrated (*cf.* table 15) by the data for isopropylbenzene (168) and *tert*-butylbenzene.) Finally, the radicals C_6H_5, *p*-ClC_6H_4, and *p*-$NO_2C_6H_4$ present a sequence of increasing electrophilic nature, and hence would be expected to show increasing meta substitution of $C_6H_5CCl_3$, assuming steric hindrance to remain constant in the series; this is strikingly demonstrated by the reported data (see table 4 of reference 92).

For substitution in nitrobenzene the influence of the attacking radical was demonstrated by Hey, Nechvatal, and Robinson (164), who showed that while reaction with *p*-tolyl radicals gave rise to a mixture containing 9 per cent of 4'-methyl-3-nitrobiphenyl, this proportion was increased to about 12 per cent when *p*-bromophenyl radicals were used. These tendencies, which are in agreement with the theory of substituted radicals which has been developed, are confirmed by more recent measures of the ratio of isomers obtained in the arylation of nitrobenzene. Thus, it has been shown (146) that with *p*-nitrophenyl radicals the isomers are formed in the proportions ortho 57.5 per cent, meta 15.2 per cent, para 27.3 per cent. With *p*-bromophenyl radicals (55), the ratio of isomers is ortho 58.8 per cent, meta 13.4 per cent, para 27.8 per cent.

For aryl radicals other than phenyl the overall reaction is determined, therefore, by the relative electron charge configurations of both the reactants, as well as the corresponding homolytic reactivities of the individual solvent positions. In comparison of theoretical predictions based on quantum-mechanical calculations with experimental data for homolytic reactions, the only investigations which have any significance are those in which nearly neutral radicals participate, i.e., the phenylation reactions. Even here, some electrical effects may be present (251, 281), but it is the best case that can be treated experimentally. It is regrettable that simple alkyl radicals have not so far proved amenable to quantitative investigations of this type, as these, too, should be almost neutral. Most other radicals, such as trichloromethyl and other substituted alkyl radicals and hydroxyl radicals, must be highly polarized, and hence entirely unsuitable for the determination of the factors influencing the reactions of neutral free radicals.

D. HYDROXYLATION

The interpretation of the results of hydroxylation experiments (67, 203, 213–215, 231, 261–266), which are very complicated and somewhat uncertain, is extremely difficult (288). The isomer ratios obtained in apparent substitution of aromatic compounds seem to be dependent on experimental conditions, e.g., the pH of the solution, and often the simple monohydroxylated compound comprises only a minor portion of the total product (213, 214). The relevant isomer ratios are given in tables 8 and 9 of the accompanying paper (92).

TABLE 18*

Partial and total relative rate factors for phenylation at 80°C.

Aromatic Compound	${}^{X}_{H}k_o$ or ${}^{X}_{H}k_\alpha$	${}^{X}_{H}k_m$ or ${}^{X}_{H}k_\beta$	${}^{X}_{H}k_p$ or ${}^{X}_{H}k_\gamma$	${}^{X}_{H}K$
$C_6H_5NO_2$	6.86	1.20	7.68	4.00
C_5H_5N	1.81	0.87	0.87	1.04
C_6H_5F	2.19	1.50	1.23	1.35
C_6H_5Cl	2.60	1.12	1.19	1.44
C_6H_5Br	2.09	1.80	1.83	1.75
C_6H_5I	2.08	1.71	1.80	1.80
C_6H_5CN	6.48	1.08	6.48	3.60
$C_6H_5CH_3$	3.5	1.0	1.4	1.68
$C_6H_5C_2H_5$	1.97	1.04	1.41	1.24
$C_6H_5C_3H_7$-*i*	0.81	1.1	1.41	0.87
$C_6H_5C_4H_9$-*t*	0.63	1.28	1.41	0.87
$C_6H_5C_6H_5$	2.91	1.38	3.42	4.00
$C_{10}H_8$	29.90	5.48	–	23.90
$C_6H_5SO_2CH_3$	2.39	1.49	1.26	1.50
$C_6H_5CF_3$	0.59	1.2	2.4	0.99
$C_6H_5Si(CH_3)_3$	0.99	1.4	1.5	1.06

* Competitive results from table 8; ratios of isomers from table 15

VII. PARTIAL RATE FACTORS FOR PHENYLATION AT 80°C.

A. RESULTS AND DISCUSSION

1. In the preceding sections the nature of the recent experimental work has been discussed. It has been found possible to determine the relative rates of phenylation of certain molecules C_6H_5X, and the proportions in which the corresponding isomers $XC_6H_4C_6H_5$ have been formed at the reaction temperature of 80°C. From these data the partial rate factors are evaluated (see Sections IV,B,6, V, and VI). Table 18 presents the results; the reader is referred to the immediately preceding sections for the arguments whereby the validities of the experiments are considered.

For all the cases investigated, except where steric hindrance is important (see Section VII,A,4), it is seen that the introduction of the X group has activated the nucleus for homolytic substitution of the near-neutral phenyl radical. The ortho and para positions display the effect better than the meta position, which is relatively unaffected by the presence of the directing group X and is, therefore, in all cases, similar in reactivity to any position in benzene. These results indicate the reason why the meta isomer was rarely observed in the early work (see table 3). It is seen that this isomer does, in fact, form a considerable fraction of the product, even when electrical and steric hindrance effects are absent (see Section VI,C), but not enough to rival the production of ortho isomer. The para isomer is generally by far the least soluble and hence is very easily isolated.

The very large proportion of ortho isomer (*cf.* tables 15 and 18) is in complete contrast to the situation as known before 1951, when only on careful investigation (*cf.* table 3) is the isomer shown to be present in any significant quantity, and then only in two or three cases. Examination of the data given in tables 5 and 7 reveals that, with one or two exceptions, the high values of ${}^{X}_{H}k_o$ are predicted by both theoretical methods. However, Rondestvedt and Blanchard

(251) have suggested an alternative explanation based on the inductive effects of the groups X. These workers postulated that in the formation of the preliminary π-complex which they envisage as the precursor of the σ-complex (*cf.* Section V,D), the phenyl radical tends to become associated with sites of high electron density, i.e., that the phenyl radical is somewhat electrophilic. In compounds C_6H_5X, in which X is a $-I$ group (e.g., $C_6H_5NO_2$), the greatest electron density is at the substituent itself, and if the postulate is accepted, the incoming radical becomes associated in the π-complex largely with the substituent X, giving a complex which can most readily rearrange to the ortho σ-complex. With $+I$ groups (e.g., CH_3), the greatest electron density is thought to be at the ortho position, and it is considered that, for this reason, the ortho σ-complex is the most easily formed in these compounds. The low value of ${}^{X}_{H}k_o$ for benzotrifluoride (*cf.* table 18) is thought to be due to the fact that in this compound the inductive effect of the trifluoromethyl group is considered to cause the electron densities to decrease in the order $p > m > o$. Steric hindrance cannot be responsible in this case, since the trifluoromethyl group is of the same size as the methyl group.

Closer examination, however, reveals certain inconsistencies in this explanation. Thus with $-I$ directing groups not only is a negative charge induced on the group itself, but also a positive charge is induced at the ortho position, and this must tend to deter the electrophilic phenyl radical from attacking this position. Again, with $+I$ directing groups, the positive charge is induced on the group X, and a corresponding deterrence must exist towards association of the radical with this position. Thus it is implicit in Rondestvedt and Blanchard's explanation that with $-I$ directing groups the charge induced at the directing group is more important than that induced at the ortho position, while with $+I$ groups, the charge induced at the ortho position is more important than that induced at the substituent itself. This is acceptable only if the $\pm I$ effects of the directing groups are largely inductomeric in nature, i.e., they are called into play by the approaching reagent and can assist, but never hinder, reaction (*cf.* Section II,C,1).

2. The magnitude of the ${}^{X}_{H}K$ value for phenylation should be compared with that for heterolytic nitration (*cf.* table 1) It is seen that the term never assumes the proportion observed in nitration, i.e., powers of ten are absent. This indicates the absence of strong Coulombic effects in the phenylation reaction.

3. The good agreement between the predicted ${}^{X}_{H}k$ values of tables 5 and 7 and the above experimental ones (table 18) is open to the criticism that, as free-radical ${}^{X}_{H}k$ values differ only slightly from unity, any set of parameters may be used in the evaluation of the predicted data This may be true, but it is equally true that this comment is somewhat out of context. The most striking thing about these predictions is the fact that they were largely made at a time when no experimental evidence whatever was available for the rates of homolytic substitution in the molecule C_6H_5X (see Section IV). The parameters were chosen to describe qualitatively the ionic forms of substitution, and the results for homolytic reaction were purely supplementary. Now, experiment has shown the prediction to be correct to a high degree of accuracy in suggesting the activating

influence of group X in all cases. This remarkable correspondence between molecular orbital theory and experiment has also been noted recently in connection with the Diels–Alder (34–41) reaction and methylation experiments (71). It would be expected that relative reactivities between different positions within a given molecule might be qualitatively assessed, but to be able to predict the actual rate of reaction of any position relative to a standard is a noteworthy achievement, particularly in view of the number of assumptions that it is necessary to accept (*cf.* Section IV).

4. (i) The comparison of the actual with the calculated partial rate factors is worthy of comment. For the case of chlorobenzene Wheland (290) found considerable difficulty in choosing parameters which would correctly predict ortho–para nitration in a deactivated nucleus. If it is assumed that this correctly limits the numerical values of the parameters, then a better correspondence in the homolytic figures (tables 7 and 18), would be expected.

(ii) The experimental results for pyridine seem somewhat low; this may be due to the fact that too low a value for $^{X}_{H}K$ has been taken (*cf.* columns (1) and (2) of table 8). It is apparent that there is not much activation in the molecule.

(iii) The experimental values for nitrobenzene show some differences from the calculated figures, but these could be minimized by correct choice of parameters and/or more accurate determination of the isomer percentages (Section VI,A).

(iv) Naphthalene presents the most interesting result. Both theoretically and experimentally this case must be further examined. It is clear, from all sides, that the molecule is very reactive. The formation of unexpected products in the phenylation reaction (1) (*cf.* Section V,B,8) casts some doubt on the meaning of the experimental results. Theoretically, the free-valence treatment (*cf.* table 5) predicts rate values of the correct magnitude, whereas that of Wheland (table 7) gives values much too large (this also applies to the prediction of electrophilic reactivity by this method; *cf.* table 6). These anomalies might be due to the neglect in the mathematical treatment of the differences between the C_9 and C_{10} atoms and the other carbons (*cf.* Sections IV,C, D, and E).

(v) The case of *tert*-butyl is especially interesting (50). Earlier it was shown that *p*-xylene, in undergoing side-chain attack, became less reactive in nuclear phenylation when compared with benzene (see Sections V,B,6 and VII,B,2). The single *tert*-butyl group shows the same effect but for entirely different reasons. Firstly, since the hyperconjugation of the *tert*-butyl group with the ring is very small, the activating effect of this group for homolytic substitution should likewise be small (*cf.* Sections IV,C,4 and IV,D,1), and the total relative rate would be expected to be of the order of $^{t\text{-}C_4H_9}_{H}K \sim 0.9$–$1.1$. Secondly, no side-chain attack of the kind observed with the other alkylbenzenes can take place (139, 204), since there are no α-hydrogen atoms and benzyl-type radicals cannot be formed under any circumstances. Thus, the competitive experiments are directly valid and there is no need, as shown experimentally, to correct for this alternative reaction. Lastly, the large size of the *tert*-butyl group might be expected to give rise to a steric effect, which in mainly affecting the generally most reactive ortho positions should cause the total relative rate to decrease. The presence of

TABLE 19

Isomer percentages obtained in nitration and phenylation of alkylbenzenes (31, 50, 168, 196, 240)

Reaction	Isomer	$C_6H_5CH_3$	$C_6H_5C_2H_5$	$C_6H_5C_3H_7$-*i*	$C_6H_5C_4H_9$-*t*
ation	Per cent ortho	57	55	30	11.8
	Per cent meta	3	0	7.7	8.7
	Per cent para	40	45	62.3	79.5
ylation	Per cent 2-phenyl	66.5	53	31	24
	Per cent 3-phenyl	19.2	28	42	49
	Per cent 4-phenyl	14.3	19	27	27

these effects has been demonstrated by the fact that substitution in benzene by the ortho *tert*-butyl radical can be effected only with great difficulty, as hydrogen abstraction is the preferred reaction (50). The combination of these processes leads to the observations (*cf.* table 18) that the ortho positions are apparently unreactive for substitution and that the total relative rate is less than unity, i.e., ${}^{t\text{-}C_4H_9}_{\;\;H}K < 1.0$.

The effect of steric hindrance is also apparent in the phenylation of phenyltrimethylsilane (251), though here it is less apparent, owing to the fact that the methyl groups are held further from the ring and consequently exert a smaller steric influence in this compound.

(vi) Similar considerations apply to the case of isopropylbenzene (168, 250) except that, in this case, side-chain attack proceeds to a considerable extent. When due allowance has been made for the side-chain attack it again becomes clear that steric hindrance to substitution at the ortho position results in a relative rate of less than unity (*cf.* table 8). A comparison (table 19) of the isomer percentages for phenylation of the alkylbenzenes with those for nitration of these compounds (31, 196) reveals a striking similarity between the steric effects observed in these reactions. In both reactions the steric effect is absent in toluene and ethylbenzene and important in isopropylbenzene and *tert*-butylbenzene.

5. An important conclusion arising from the agreement between the data of tables 5 and 18 is that there appears to be some support for assuming the value of $x = 1$ in Section IV,C,5 (equations 46 and 47), i.e., the r^{th} atom is completely removed from the π-bonding of the molecule and a covalent bond can be assumed to be formed in the transition complex (figure 2). This also adds weight to the decision to regard the substitution as being effected via an addition process (Sections III, IV, and VI,D).

B. ADDITIVITY OF ENERGIES OF ACTIVATION

1. Experimental verification

In Section IV,B,7 it was shown that experiments made with mono-, di- and trisubstituted benzene would allow, via equations 31, 36, and 37, the individual partial rate factors ${}^{X}_{H}k_o$, ${}^{X}_{H}k_m$, and ${}^{X}_{H}k_p$ to be obtained, provided it was assumed that the energy of activation for phenylation at any position was composed of the summation of the energies dictated by each of the X groups and their relative positions.

Owing to the doubtful validity of the methylbenzene experiments (see Sections V,B,7 and VII,B,2), this series of compounds cannot be used. The chlorobenzene sequence, however, is free from these objections, as far as is known (6), and the ${}^{\mathrm{X}}_{\mathrm{H}}K$ values recorded in table 8 are substituted into the appropriate equations mentioned above. Unfortunately, no positive root to the derived cubic equation is obtained but, by assuming separate errors of ca. 20 per cent in ${}^{s\text{-}\mathrm{Cl}_2}_{\mathrm{H}}K$, 10 per cent in ${}^{p\text{-}\mathrm{Cl}_2}_{\mathrm{H}}K$, or 3 per cent in ${}^{\mathrm{Cl}}_{\mathrm{H}}K$, or simultaneous smaller errors in each, the curve can be displaced vertically to give a positive root. This is not an unreasonable assumption, since the single error of 3 per cent required in the value of ${}^{\mathrm{Cl}}_{\mathrm{H}}K$ is within the limits of accuracy of the determination. Solution of the cubic equation then gives:

$${}^{\mathrm{Cl}}_{\mathrm{H}}k = 2.7; \qquad {}^{\mathrm{Cl}}_{\mathrm{H}}k_m = 1.49; \qquad {}^{\mathrm{Cl}}_{\mathrm{H}}k_p = 1.05 \qquad (58)$$

These results illustrate the fact that small experimental deviations may prevent any answer from being obtained In the light of the assumptions made, however, the results are good. The figures of equation 58, when compared with the partial rate factors of table 18, suggest that the important assumption, made above, as to the additivity of the energies of activation, is correct (6). This might have been expected by analogy with heterolytic substitution (27, 200, 201, 246). Other methods for checking these conclusions for the homolytic case are available but have not so far been applied.

2. *Application of principle*

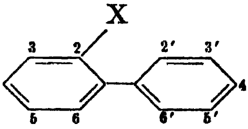
If the above conclusion is accepted, the principle of the additivity of the energies of activation may be employed in useful explanation and prediction. If the partial rate factors for groups X and Y are available, then for the molecule r-YC$_6$H$_4$X the reactivity of any position, or the total reactivity, may be obtained by the method described in Section IV.

(i) Returning to the methylbenzenes (1) (Section V,B,7), and using this principle in the form of equations 36 and 37 with the ${}^{\mathrm{CH}_3}_{\mathrm{H}}k_r$ values for toluene from tables 7 and 18, the calculated values for the total relative rates are:

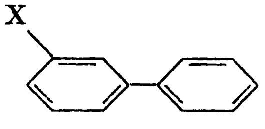
$$\left.\begin{array}{lllll} \mathrm{X} = \mathrm{CH_3} & p\text{-}(\mathrm{CH_3})_2 & s\text{-}(\mathrm{CH_3})_2 & & \\ {}^{\mathrm{X}}_{\mathrm{H}}K = 1.48 & 1.44 & 6.74 & \text{value of } {}^{\mathrm{CH}_3}_{\mathrm{H}}k_r \text{ taken} \\ & & & \text{from table 7} \\ {}^{\mathrm{X}}_{\mathrm{H}}K = 1.85 & 2.53 & 11.60 & \text{value of } {}^{\mathrm{CH}_3}_{\mathrm{H}}k_r \text{ taken} \\ & & & \text{from table 18} \end{array}\right\} \qquad (59)$$

These series should be compared with the observed sequence (equation 56), which makes allowance for side-chain attack. This observed order, if it is a true one, can be explained by the following. It is seen from equation 59 that the methyl group in toluene slightly activates the five nuclear positions and nuclear substitution is statistically favored. Xylene is only slightly more active than toluene, since every position is meta to a methyl group and ${}^{\mathrm{X}}_{\mathrm{H}}k_m$ values are usually of the order of unity (*cf.* table 18). Hydrogen removal is encouraged by the methyl groups owing to their size, and since the nucleus is not sufficiently activated, this side-chain attack predominates. In mesitylene, the introduction of the third methyl group has caused the nucleus to become highly reactive as each position is both ortho and para to a methyl group, and direct substitution is again favored but has to compete with side-chain attack (see Section V,B,7). Similar argument is applied to the case of *p*-di-*tert*-butylbenzene (50).

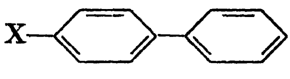
(ii) The above technique may be applied to molecules containing dissimilar directing groups X and Y and is very important in permitting predetermination of experiment. Consider molecules of the type *r*-$C_6H_5C_6H_4X$, e.g., the isomeric phenylpyridines or nitrobiphenyls (80). Using the known partial rate factors for chlorobenzene, nitrobenzene, pyridine, and biphenyl (*cf.* table 18), and making the reasonable assumptions given in the footnote to table 20, the figures given in tables 20 and 21 may be evaluated for the reactivities of the isomers shown in formulas A, B, and C:



A



B



C

It is seen that the difference in reactivities of the phenylpyridines is small. Any experiment using a mixture of such compounds, e.g., that which is formed on phenylation (*cf.* table 15: A = 58 per cent, B = 28 per cent, and C = 14 per cent), designed to study whether or not such isomers are selectively removed by further

TABLE 20*

Composite partial rate factors for phenylation at 80°C.

X	Isomer A				Isomer B				Isomer C	
	k_3	k_4	k_5	k_6	k_2	k_4	k_5	k_6	k_2 or k_6	k_3 or k_5
Hetero nitrogen	2.66	3.03	1.48	2.58	5.51	6.46	1.25	3.07	2.58	2.66
Chlorine	3.64	3.81	1.67	3.25	7.54	8.84	1.57	3.45	3.25	3.64
Nitro	9.74	4.08	10.75	3.48	20.18	23.66	1.68	22.27	3.48	9.74

* Assuming that the group XC_6H_4—is similar to an unsubstituted group in its effect on the nucleus to which it is attached, the partial rate factors for positions 2′–6′ (formulas A, B, and C above) have the same values as the partial rate factors for these positions in biphenyl (table 18). The data of table 21 may then be obtained by addition.

TABLE 21

Calculated relative rates of phenylation of isomeric X-biphenyls at 80°C.

	$^{XC_6H_4}_{H}K$ for A	$^{XC_6H_4}_{H}K$ for B	$^{XC_6H_4}_{H}K$ for C
Hetero nitrogen.	3.62	4.71	3.75
Chlorine.	4.06	5.57	4.30
Nitro.	6.68	13.30	6.57

phenylation, must consequently be capable of high accuracy. Thus, the reported work (80) indicating no such effect (see Sections V,A,3, V,B,4, and VI,B), wherein 22 per cent of the original mixture of phenylpyridines was phenylated, should have been capable of working to an accuracy of better than 1.5 per cent on the percentages of isomers A and B if it were to yield the required information. This was not the case, and the experiment is therefore inconclusive. On the other hand, the employment of a similar mixture of nitrobiphenyls, artificially enriched in the meta isomer B, would have allowed an experimental accuracy of 5 per cent, a result which is feasible.

VIII. CONCLUSIONS

Throughout the previous sections the various conditions upon which the significance of the developed partial rate factors depend have been analyzed and discussed.

The topic of homolytic aromatic substitution is a large one. Theoretical techniques are capable of only very approximate results, and the practical difficulties encountered in experimental work are many and formidable. Owing to the delicate fashion in which the reactions appear to be balanced, such that almost any reaction has some probability of fulfilment, the subject has to be carefully broken down and any discussion carefully qualified.

The competitive method has been used to obtain total relative rate values for phenylation. In certain cases, where steric and other effects become important, it is necessary to declare the results invalid for comparison with mathematical theory, e.g., the methylbenzenes and phenol. The results of different workers are in agreement. From the classification of aromatic solvents into orders of reactivity, it is possible to explain the variation in product quantities and the appearance of reduction products in the mixture. These phenomena concur with the observed kinetics of benzoyl peroxide decomposition. The mechanism of this decomposition is discussed with reference to the nature of the solvent present. Except for specific cases (phenols, amines, methylbenzenes, and anisole), the predominance of the reaction:

$$C_6H_5X + C_6H_5\cdot \rightarrow C_6H_5C_6H_4X + \cdot H$$

as initially suggested by Hey, is shown to be substantiated. Substitution is effected by the radical $C_6H_5\cdot$ itself, probably through an addition mechanism. It is impossible to say whether or not the hydrogen atom is ever free. The alternative reaction involving hydrogen-atom abstraction from the aromatic nucleus occurs only very rarely, but hydrogen-atom removal from a side chain may take place (particularly with phenol and alkylbenzenes), sometimes to the exclusion of the nuclear substitution reaction. The first examples of side-chain attack by aryl radicals in solution are presented.

Together with recent accurate data concerning the proportions in which the isomers are formed in the phenylation of C_6H_5X, the competitive reaction results allow the partial relative rate factors for phenylation to be derived. These values are probably the nearest that can be obtained to those representing true homolytic attack of a neutral free radical upon the molecule C_6H_5X. The data presented confirm the existence of homolytic substitution and place the treatment upon a quantitative basis.

A review of the more recent theories of aromatic substitution has shown that the difficulties which these methods encountered were to some extent due to the fact that they had to operate upon experimental data which were representative only of heterolytic reactions. The modifications which have been made, and the new treatments which have been devised in order to describe free-radical phenomena, have been described and presented in a critical manner. Although they were developed at a time when the relevant experimental data were not available, certain of these treatments allow the quantitative behavior of homolytic phenomena to be predicted. These predictions are discussed.

A comparison between the experimental partial relative rate factors for phenylation and those predicted for homolytic substitution shows a high degree of agreement. The evidence is in favor of the formation of a covalent bond in the transition state of the reaction, with the consequent removal of the attacked site from the delocalization area of the solvent molecule. All theories have indicated that, for true free-radical attack, provided complicating effects are absent, the nucleus of C_6H_5X is always activated relative to benzene, with ortho substitution predominating. This has been verified experimentally by the phenylation experiments, carried out in systems relatively free from any electrical, steric, and other complicating effects. This, therefore, presents a guiding rule for neutral homolytic substitution. Meta-substituted compounds are produced, the position being only slightly more active than any one position in benzene, unless complicating effects are present when meta-substituted compounds may form the majority of the product mixture. The observed activations are compared with those observed in electrophilic reactions and are found to be of a lower order of magnitude.

The radical–environment relationship has been discussed. The consideration of other radicals, i.e., aryl (not phenyl), acyloxy, and hydroxyl, must include a study of the demands of the reagent, for these may determine the form of the reactions with any of the typically aromatic solvents. Electrical effects have been shown to be present, and it is possible to speak of electrophilic and nucleophilic free radicals. Here the effects due to electrical polarization and to the odd electron are superimposed.

The need for much further theoretical and experimental work is apparent and certain lines of research have been suggested in the presentation. A concentration of effort upon reactions of homolytic nature will, undoubtedly, allow theoretical interpretations to be adequately tested. Studies of this nature will permit further investigation of the electrical effects in the substitution and this may, by extrapolation, be related to the case of heterolytic substitution.

While the ultimate goal of investigations of this type must be the complete understanding of the substitution reaction in aromatic systems, it is unlikely that precise prediction of the course of the reaction will become possible, on account of the extreme difficulties of accurate mathematical treatment.

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ADDENDUM

This review was completed in February, 1956. The articles referred to in references 168 and 170 have since then appeared in print. Other recently published work relevant to the subject is noted below. Some of these papers, especially those of Batten (300) and Batten and Mulcahy (301), are of particular importance to the main discussion.

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RECENT DEVELOPMENTS IN THE SYNTHESIS OF FATTY ACIDS

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Received May 11, 1956

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I. INTRODUCTION

A significant amount of new information on the synthesis of fatty acids has accumulated since Gunstone in 1953 (148) and Breusch in 1950 (58) published their reviews. It seemed desirable, accordingly, to make available a more up-to-date summary of the field. The first steps were taken in connection with a talk given by the author at a Gordon Research Conference on Fats and Oils in September, 1955. The present paper is a formalized and considerably expanded version of this talk.

The chemistry of fatty acid synthesis is treated here in two parts, the first dealing with pertinent methods and the second with specific acids. Emphasis is placed on the literature of 1950 through 1955, although by no means to the exclusion of other relevant material. Syntheses of and synthetic methods for the preparation of linear, branched, ethylenic, acetylenic, hydroxy, cyclic, and various other kinds of fatty acids containing ten or more carbon atoms are included. The synthesis of polybasic or of aromatic acids has not been covered.

From the synthetic point of view, probably the most interesting development in the last ten years is the increasing importance of the acetylenic bond. The synthesis of fatty acids has leaned heavily on acetylene chemistry. Some idea of how extensive this application of acetylene chemistry is may be obtained from the fact that approximately one out of every three papers consulted for this review in some way involved the triple bond. A recent book by Raphael (232) ably summarizes the chemistry of acetylenic compounds and makes available an authoritative and timely compilation of useful information.

The overwhelmingly preponderant part of the total fatty acids in nature is accounted for by a small number of acids, such as oleic, linoleic, palmitoleic, palmitic, and a few others (158). These fatty acids are all more or less similar in structure. Considerable diversity in fatty acid structure is found, however, in the many acids comprising but a minor percentage of the total. Many in this group of minor fatty acids, the members of which occur often in only a single plant or animal species and there, not infrequently, in surprisingly high concentration, are interestingly and significantly different from the predominant acids. These minor acids have attracted much attention and, as is evident in the following pages, have stimulated much synthetic work.

The nomenclature of fatty acids is encumbered with trivial names. A list of the more common names used in this report together with their systematic equivalents follows.

Common Name	Systematic Equivalent
Elaidic acid	*trans*-9-Octadecenoic acid
Linoleic acid	*cis*-9,*cis*-12-Octadecadienoic acid
Oleic acid	*cis*-9-Octadecenoic acid
Palmitic acid	Hexadecanoic acid
Palmitoleic acid	*cis*-9-Hexadecenoic acid
Stearic acid	Octadecanoic acid
Stearolic acid	9-Octadecynoic acid
Undecylenic acid	10-Undecenoic acid

Generally, numbering in the names of fatty acids starts with the carboxyl carbon, which is assigned the 1-position. However, no hesitation has been felt in writing α, β, γ to designate the 2-, 3-, and 4-positions, respectively, when usage or clarity affords a reason for so doing.

II. SYNTHETIC METHODS

A. INTRODUCTION OF CARBOXYL GROUP

Oxidative processes have been involved in forming the carboxylic function. For example, 10-undecenoic acid (*cf.* 63) and 10-undecynoic acid (39) have been converted, respectively, to 9-decenoic acid and 9-decynoic acid by Grignard addition to the ester, dehydration, and oxidative cleavage (Barbier–Wieland degradation). Saturated acids are converted cleanly to the next lower homologs by the following steps: α-bromination, hydrolysis (directly or indirectly) to α-hydroxy acid, and finally oxidative cleavage with excess lead tetraacetate in the presence of air (162a, 203b; also see 115a; *cf.* Section II,O,3). Oxidation of aldehydes or of primary alcohols can give the corresponding carboxylic acids. A mixture of dilute sodium hydroxide and silver nitrate constitutes the favorite reagent for the oxidation of aldehydes (33, 218, 236, 287). Permanganate has been used in the oxidation of 6-methyloctyl alcohol to 6-methyloctanoic acid (111), but the more common alcohol-oxidizing reagent is hexavalent chromium (38, 47, 60, 61, 96, 177, 192). Formulas I and II show how acetylenic and even ethylenic unsaturation can survive the conditions of such oxidation. The oxidation of primary alcohols to aldehydes is discussed in Section II,B.

$$\mathrm{CH_3CH{=}CHC{\equiv}CC{\equiv}CCH{=}CHCH_2OH} \quad \mathrm{CrO_3}$$

I

$$\mathrm{CH_3CH{=}CHC{\equiv}CC{\equiv}CCH{=}CHCOOH}$$

II

With alkyl halide available, [illegible]nation of the Grignard derivative or combination with cyanide followed [illegible]drolysis constitutes two familiar methods of extending the chain by one carbon atom while introducing carboxyl. These two methods, together with the malonate sequence, probably are the most frequently encountered reactions in the entire field of acid synthesis. Both the Grignard carboxylation and the nitrile synthesis afford opportunity for the introduction of isotopic carbon, not only in the carboxyl position but also in the hydrocarbon chain of the fatty acid (*cf.* 165; also Section II,O,5). For example (116), 6-labeled palmitic acid (III) was prepared by carbonating decylmagnesium bromide with radioactive carbon dioxide, and then adding five carbon

$$CH_3(CH_2)_9MgBr \xrightarrow[(2)\ H_2O]{(1)\ C^{14}O_2} CH_3(CH_2)_9C^{14}OOH \rightarrow \cdots \rightarrow$$

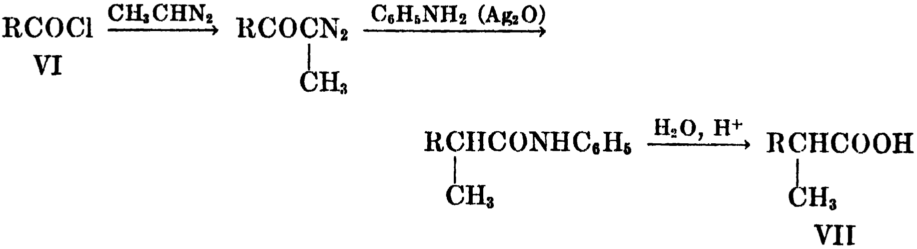
$$\underset{\text{III}}{CH_3(CH_2)_9C^{14}H_2(CH_2)_4COOH}$$

atoms by standard methods. Carbonation of acetylenic Grignard reagents (or their sodium derivatives) is a reliable and convenient method of adding carboxyl to a terminal acetylene group and simultaneously of introducing α,β-unsaturation. Closely related to carbonation is the reaction of Grignard reagents, either saturated or acetylenic, with ethyl orthoformate to give (after hydrolysis) aldehydes containing one more carbon atom than the starting material (see Section II,B). Whether the carbonation of alkenyllithium (56; also *cf.* 57) or alkenyl Grignard derivatives (220) receives extensive use in the synthesis of fatty acids remains to be seen. In reactions of sensitive alkyl bromides, substitution of cuprous cyanide in an inert solvent for the more usual alkali metal cyanide in aqueous alcohol has proved expedient (92). Another modification is the reaction with sodium cyanide in slightly acid medium (45). For example, the conversion

$$\underset{\text{IV}}{HC{\equiv}C(CH{=}CH)_2CH_2Br} \xrightarrow[\text{pH 3-6}]{\text{NaCN (Cu)}} \underset{\text{V}}{HC{\equiv}C(CH{=}CH)_2CH_2CN}$$

of the triunsaturated allyl bromide IV to nitrile V called for the use of sodium cyanide in the presence of copper powder in aqueous tetrahydrofuran at pH 3–6.

Arndt–Eistert homologation provides a method for extending the carbon chain at the carboxyl end of an acid, which may be either saturated or unsaturated (22, 33, 123, 182, 195, 225, 226, 284, 297). The noteworthy possibility of introducing α-methyl by the use of diazoethane is illustrated by the conversion of acid chloride VI to α-methyl acid VII (32).

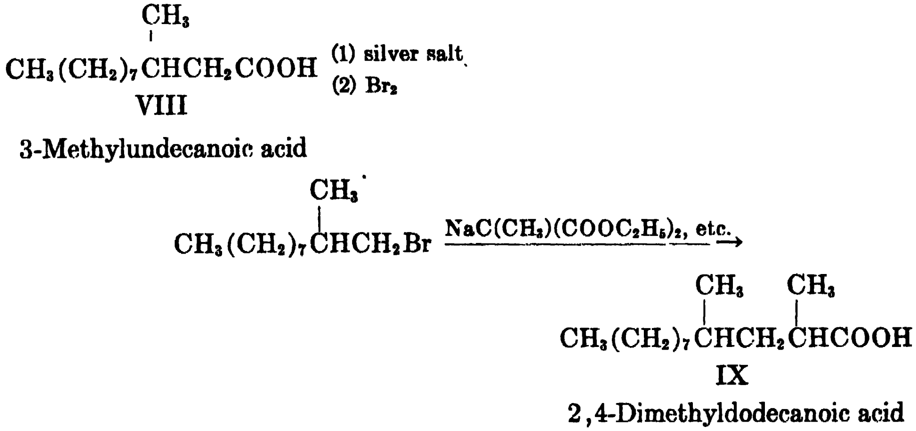


$$\underset{\text{VI}}{RCOCl} \xrightarrow{CH_3CHN_2} RCO\underset{\displaystyle CH_3}{\underset{|}{C}}N_2 \xrightarrow{C_6H_5NH_2\ (Ag_2O)}$$

$$R\underset{\displaystyle CH_3}{\underset{|}{C}}HCONHC_6H_5 \xrightarrow{H_2O,\ H^+} R\underset{\displaystyle CH_3}{\underset{|}{C}}HCOOH$$

VII

Another method for extending an acid chain by one carbon atom and at the same time introducing a branch at the new α-position proceeds by decarboxylation by means of a silver salt and bromine, followed by a malonic ester sequence with *methylmalonic* ester (*cf. inter alia* 69, 77, 177, 290). In this way, for example, 3-methylundecanoic acid (VIII) was converted to 2-methyldecyl bromide and



$$CH_3(CH_2)_7\overset{CH_3}{\overset{|}{C}}HCH_2COOH \xrightarrow[(2)\ Br_2]{(1)\ \text{silver salt}}$$

VIII

3-Methylundecanoic acid

$$CH_3(CH_2)_7\overset{CH_3}{\overset{|}{C}}HCH_2Br \xrightarrow{NaC(CH_3)(COOC_2H_5)_2,\ \text{etc.}}$$

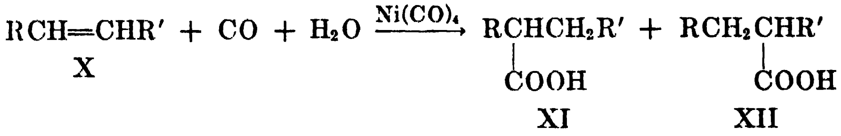
$$CH_3(CH_2)_7\overset{CH_3}{\overset{|}{C}}HCH_2\overset{CH_3}{\overset{|}{C}}HCOOH$$

IX

2,4-Dimethyldodecanoic acid

then with diethyl sodiomethylmalonate to 2,4-dimethyldodecanoic acid (IX) (69). Use of unsubstituted malonic ester results in overall simple homologation.

Olefins (X) or alcohols with carbon monoxide and water under pressure and in the presence of nickel or nickel carbonyl give carboxylic acids (XI and XII).



$$RCH{=}CHR' + CO + H_2O \xrightarrow{Ni(CO)_4} R\underset{COOH}{\underset{|}{C}}HCH_2R' + RCH_2\underset{COOH}{\underset{|}{C}}HR'$$

X XI XII

Other variations lead directly to acid derivatives such as esters, amides, anhydrides, etc. (3; 99, p. 266; 238, 239). Nickel carbonyl with acetylenes gives α,β-unsaturated carboxylic acids (179, 237). In a related process olefins with carbon monoxide and hydrogen in contact with cobalt carbonyl give saturated aldehydes (154; 99, p. 280).

Many of the reactions discussed in the following pages result in insertion of the carboxyl group. It is more convenient to consider these methods under other section headings; hence such methods are not treated here.

B. REACTIONS WITH ALDEHYDES

Long-chain aldehydes can be used for the preparation of fatty acids or more generally for chain extension. Thus, oxidation gives the corresponding carboxylic acid (Section II,A). Reformatsky condensation gives β-hydroxy esters (Section III,H,5). Condensation with malonic acid gives α,β-unsaturated acids (Section II,O,3). Combination with alkylidene-triphenylphosphine in the Wittig–Geissler process gives olefins (Section II,N). Reaction with propargylmagnesium or zinc derivatives gives hydroxy acetylenes (Section II,D). Grignard addition offers the possibility of combining two large fragments. In this last way, for example, 5,5-dimethylhexylmagnesium chloride (XIII) with 15-carbethoxypentadecanal gave a hydroxy ester (XIV), which could be converted in a straightforward

$$(CH_3)_3C(CH_2)_4MgCl + O{=}CH(CH_2)_{14}COOC_2H_5 \longrightarrow$$

XIII

$$(CH_3)_3C(CH_2)_4CHOH(CH_2)_{14}COOC_2H_5$$

XIV

$\downarrow$ (1) saponification
(2) PBr_3
(3) 20% alcoholic KOH
(4) H_2, Pt

$$(CH_3)_3C(CH_2)_{19}COOH$$

21,21-Dimethyldocosanoic acid

manner to 21,21-dimethyldocosanoic acid (259; also *cf.* 13, 159, 184, 286). The analogous series starting with a ketone instead of an aldehyde produces a branched-chain acid (*cf.* 118).

The last stages in an elegant synthesis of oenanthetol (XVI) provide a good example of extension of a chain by Grignard addition. Heptylmagnesium bro-

$$CH_3(CH_2)_6MgBr + O{=}CHCH{=}CH(C{\equiv}C)_2CH{=}CHCH_2OCOC_6H_5 \longrightarrow$$

XV

$$CH_3(CH_2)_6CHOHCH{=}CH(C{\equiv}C)_2CH{=}CHCH_2OH \xrightarrow{CH_3C_6H_4SO_3H\text{ in toluene}}$$

$$CH_3(CH_2)_5(CH{=}CH)_2(C{\equiv}C)_2CH{=}CHCH_2OH$$

XVI

Oenanthetol

mide (in excess) with aldehyde XV gave a dihydroxy intermediate. Acid-catalyzed elimination of water then gave oenanthetol (XVI) (159).

A method not yet applied extensively to the synthesis of fatty acids may be illustrated by the formation of 12-oxostearic ester (XVII) (63), which was pro-

$$CH_3(CH_2)_5CHO + CH_2{=}CH(CH_2)_8COOC_2H_5 \xrightarrow{(C_6H_5COO)_2}$$

Heptanal Ethyl 10-undecenoate

$$CH_3(CH_2)_5COCH_2CH_2(CH_2)_8COOC_2H_5$$

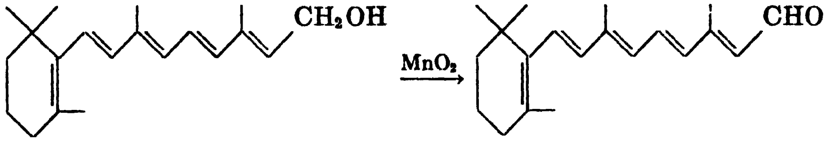
XVII

Ethyl 12-oxostearate

duced in low yield when a mixture of heptanal (excess) and 10-undecenoic ester was exposed to the action of benzoyl peroxide.

The use of aldehydes presents two problems: (*a*) preparation of the aldehyde, a procedure which is not always uncomplicated, and (*b*) the tendency of the aldehyde once formed to deteriorate by autoxidation, condensation, or trimerization. Proper handling and storage of the aldehydes and the possibility of thermal depolymerization of the trimer help to minimize loss by deterioration. Some useful or suggestive preparations for long-chain aldehydes are summarized in the following paragraphs (*cf.* 214).

Controlled oxidation of alcohols to aldehydes is feasible. Manganese dioxide has become a more or less standard reagent in converting *allyl* alcohols to α,β-unsaturated aldehydes, e.g., vitamin A (XVIII) to vitamin A aldehyde (241;



XVIII
Vitamin A

Vitamin A aldehyde

also *cf.* 44, 47, 159, 242). Hexavalent chromium under carefully specified conditions has also been used for the same purpose (174, 263), as well as for the oxidation of nonallylic alcohols to the corresponding aldehydes.

An oxidative process by which RCH_2COOH can be degraded to RCHO is formulated in Section II,O,3 (190).

Other methods used for the preparation of aldehydes include Rosenmund hydrogenation of an acid chloride over a poisoned palladium catalyst (71, 80, 150, 176, 213, 259) and the controlled reduction of an amide by lithium aluminum hydride (*cf.* 218). A two-stage process (e.g., XIX to XX) of combining ethyl orthoformate with a Grignard reagent, either alkyl or acetylenic, to yield an acetal, followed by hydrolysis with dilute acid, has proved effective in preparing

$$\underset{\text{XIX}}{CH_3CH_2CH_2CH{=}CH(CH_2)_4MgBr} \xrightarrow{HC(OC_2H_5)_3}$$

$$CH_3CH_2CH_2CH{=}CH(CH_2)_4CH(OC_2H_5)_2 \xrightarrow{H_2O,\ H^+}$$

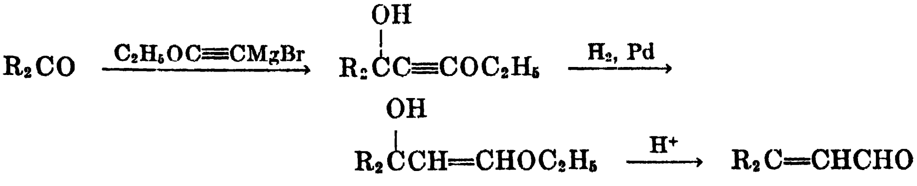
$$CH_3CH_2CH_2CH{=}CH(CH_2)_4CHO$$

XX

6-Decenal

a variety of saturated and unsaturated aldehydes (100; also *cf.* 4, 101, 104, 114, 236, 263). The oxo or hydroformylation process utilizes cobalt or cobalt carbonyl in the addition of carbon monoxide and hydrogen to an olefin to form a saturated aldehyde (154; 99, p. 280).

The addition of ethoxyacetylene to carbonyl compounds, half-hydrogenation of the triple bond, and acid hydrolysis of the resulting vinyl ether furnish an



$$R_2CO \xrightarrow{C_2H_5OC{\equiv}CMgBr} R_2\overset{\displaystyle OH}{\overset{|}{C}}C{\equiv}COC_2H_5 \xrightarrow{H_2,\ Pd}$$

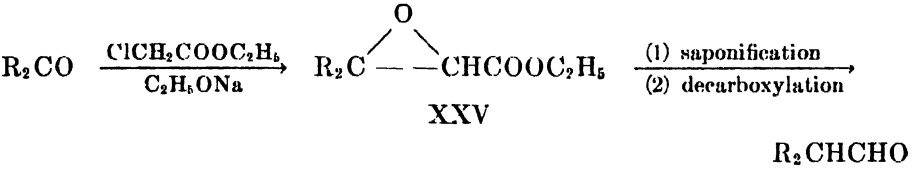
$$R_2\overset{\displaystyle OH}{\overset{|}{C}}CH{=}CHOC_2H_5 \xrightarrow{H^+} R_2C{=}CHCHO$$

XXI

α,β-unsaturated aldehyde (XXI) (*cf.* 122; 232, p. 72). In a related process the lithium derivative of ethoxyvinylacetylene (XXIII) was used to transform aldehyde XXII to aldehyde XXIV (159; also *cf.* 203a). The reduction of lauronitrile to dodecanal with stannous chloride and hydrogen chloride in ether (Stephen reduction) has been studied (193). The sequence formulated in Section III,B by which RC≡CH is converted to RCH_2CHO appears to be general (232, p. 44; also *cf.* 25), as does the method described in Section III,H,1 for converting RC≡CH to $RCH{=}CHCH_2CHO$. The general process of converting a carbonyl compound to the homologous aldehyde is accomplished by the Darzens method, that is, by condensing the carbonyl compound with chloroacetic ester and sodium ethoxide, and by saponifying and decarboxylating the resulting glycidic ester (XXV) (217).

$$\underset{\substack{\text{XXII}\\ \text{2-Hexenal}}}{CH_3CH_2CH_2CH{=}CHCHO} \xrightarrow{C_2H_5OCH{=}CHC{\equiv}CLi\ (\text{XXIII})}$$

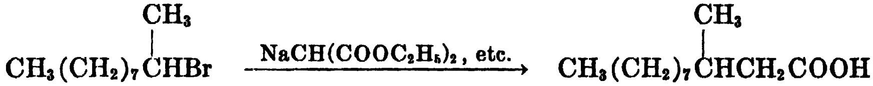
$$CH_3CH_2CH_2CH{=}CHCHOHC{\equiv}CCH{=}CHOC_2H_5 \xrightarrow[(2)\ H_2O,\ H^+]{(1)\ H_2,\ Pd} \underset{\text{XXIV}}{CH_3CH_2CH_2(CH{=}CH)_3CHO}$$


XXV

C. EXTENSION OF THE CHAIN BY TWO CARBON ATOMS

Reaction of a Grignard reagent or a metal acetylide (*cf.* 85, 101, 259) with ethylene oxide adds two carbon atoms and gives a product terminating in a primary hydroxyl group. Reaction of an alkyl halide or of a carbonyl with sodium acetylide extends the chain by two carbon atoms and presents a terminal acetylenic group for further operations. By condensing an aldehyde or a ketone with zinc and bromoacetic ester the Reformatsky process adds two carbon atoms to the chain and forms a β-hydroxy ester (Section III,II,5). Substitution of α-bromopropionic ester for bromoacetic ester places a branch on the new α-position. Condensation of aldehydes with malonic acid in pyridine solution containing piperidine (i.e., under Doebner conditions) gives an α,β-unsaturated acid containing two more carbon atoms than the starting aldehyde (Section II,O,3). An acid containing n carbon atoms can be converted to a β-keto ester containing $(n + 2)$ carbon atoms by methods outlined in Section II,J. The Kolbe cross product from a monobasic acid and methyl hydrogen succinate has two carbon atoms more than the original monobasic acid (*cf.* 288; also Section III,A).

The familiar malonic ester synthesis has been used repeatedly and efficiently for converting RX to RCH_2COOH. Secondary as well as primary alkyl bromides can be used; in one case optically active 2-bromodecane was converted to optically active 3-methylundecanoic acid (XXVI) with only minor racemization (229). Repeated sequences of the type RBr → RCH_2COOH → RCH_2CH_2OH → RCH_2CH_2Br, etc. are not uncommon. Probably the best example—one in which the sequence is used no less than six times—is in the elaboration of 15-methylpalmitic acid (XXVII) from isovaleric acid (290). Lithium aluminum hydride has been widely accepted as a convenient and effective reagent for the reduction of an acid (or ester) to an alcohol, although sodium and alcohol or high-temperature high-pressure hydrogenation (1) over a Cu-Cr-O catalyst still finds application.



$$CH_3(CH_2)_7\overset{\overset{\displaystyle CH_3}{|}}{C}HBr \xrightarrow{NaCH(COOC_2H_5)_2,\ etc.} CH_3(CH_2)_7\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2COOH$$

XXVI

2-Bromodecane

3-Methylundecanoic acid

$$(CH_3)_2CHCH_2COOH \quad \left[\begin{array}{l}(1)\ LiAlH_4\\ (2)\ P + I_2\\ (3)\ NaCH(COOC_2H_5)_2,\ etc.\end{array}\right]_6$$

$$(CH_3)_2CH(CH_2)_{13}COOH$$

XXVII

15-Methylpalmitic acid

Branching can be introduced by the dialkylation of malonic ester (22) or more generally by the alkylation of a monoalkylmalonic ester. For example, the series of 2-alkylstearic acids (XXVIII) in which the alkyl group ranged from methyl to dodecyl was prepared by this method (289; see also 21, 70, 76, 86, 290). 2,3-Dialkyl acids have been obtained by alkylating monoalkylmalonic ester with secondary alkyl bromides (120). Methylmalonic ester has been of special interest in connection with synthetic approaches to the acids from the tubercle bacillus. Here, methylmalonic ester has been used not only for introduction of the terminal $—CH(CH_3)COOH$ unit but, by a repeating series entirely analogous to that described for the synthesis of 15-methylpalmitic acid (XXVII), for the introduction of methyl branching in the middle of the chain (*cf.* Section III,F and 27, 73, 130).

$$CH_3(CH_2)_{15}I \xrightarrow{NaCR(COOC_2H_5)_2,\ etc.} CH_3(CH_2)_{15}CHRCOOH$$

XXVIII

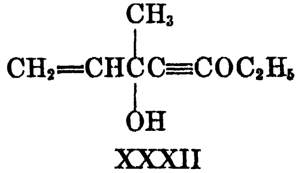
Application of the malonic ester process after degradation of RCOOH to RBr by means of a silver salt and bromine can lead to RCH_2COOH or, if monoalkylmalonic ester is involved, to RCH(R′)COOH (Section II,A).

The sodium derivative (XXIX) of ethoxyacetylene, prepared from dichloroethyl ethyl ether, has been combined with butyl bromide to give an acetylenic ether (XXX), which was hydrolyzed readily, although in low yield, to ethyl hexanoate (122). The reactions constitute an alternative to the more conventional malonic ester synthesis. The reaction of ethoxyacetylene with carbonyl compounds, e.g., methyl vinyl ketone (XXXI), is also possible (122, 180; see also 251 and 232, p. 82). The product with dilute aqueous acid smoothly gives an α,β-unsaturated ester (XXXIII). This process is an attractive alternative to the Reformatsky process. Half-hydrogenation of the intermediate acetylenic ether (e.g., XXXII) to the corresponding vinyl ether, followed by hydrolysis, yields an α,β-unsaturated aldehyde (Section II,B).

$$CH_2ClCHClOC_2H_5 \xrightarrow{3NaNH_2} \underset{\text{XXIX}}{NaC{\equiv}COC_2H_5} \xrightarrow{CH_3(CH_2)_3Br}$$

$$\underset{\substack{\text{XXX}\\ \text{Ethyl 1-hexynyl ether}}}{CH_3(CH_2)_3C{\equiv}COC_2H_5} \xrightarrow{H_2O,\ H^+} \underset{\text{Ethyl hexanoate}}{CH_3(CH_2)_4COOC_2H_5}$$

$$\underset{\substack{\text{XXXI}\\ \text{Methyl vinyl ketone}}}{CH_2{=}CHCOCH_3} \xrightarrow{BrMgC{\equiv}COC_2H_5}$$



$$\underset{\text{XXXII}}{CH_2{=}CH\underset{OH}{\overset{CH_3}{C}}C{\equiv}COC_2H_5} \xrightarrow{2\ N\ H_2SO_4} \underset{\substack{\text{XXXIII}\\ \text{Ethyl 3-methyl-2,4-pentadienoate}}}{CH_2{=}CHC(CH_3){=}CCOOC_2H_5}$$

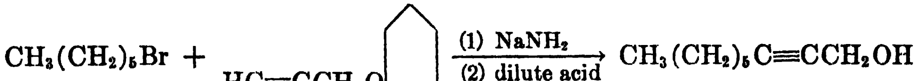
D. EXTENSION OF THE CHAIN BY THREE CARBON ATOMS

Although various three-carbon bifunctional units have been used to lengthen the chain by three carbon atoms, propargyl derivatives have been favored. For example, propargyl bromide in the presence of cuprous copper couples with acetylenic Grignard derivatives to give terminally unsaturated, "skipped" diynes (e.g., XXXIV) (139). Propargyl bromide with *alkyl* Grignard derivatives, however, gives mainly terminal allenes (*cf. inter alia* 223). Propargyl alcohol, with or without the hydroxyl group masked, presents the acetylenic hydrogen as a point of combination. Thus, in the synthesis of linolenic acid

$$CH_3(CH_2)_3C{\equiv}CMgBr + \underset{\text{Propargyl bromide}}{BrCH_2C{\equiv}CH} \xrightarrow{CuCl}$$

$$\underset{\substack{\text{XXXIV}\\ \text{1,4-Nonadiyne}}}{CH_3(CH_2)_3C{\equiv}CCH_2C{\equiv}CH}$$

(Section III,B) one pair of skipped unsaturations was developed by coupling 1-bromo-2-pentyne with the Grignard derivative of propargyl alcohol carrying a tetrahydropyranyl blocking group (218). The same tetrahydropyranyl compound, as the sodium derivative, combines smoothly with alkyl bromides to give products which with dilute sulfuric acid give 1-hydroxy-2-alkynes (e.g.,



XXXV

2-Nonyn-1-ol

XXXV) in 60–80 per cent overall yield (98). The di-Grignard derivative of propargyl alcohol in tetrahydrofuran has been combined with crotonaldehyde to yield the expected dihydroxy compound (XXXVI) (45).

$$\underset{\text{Crotonaldehyde}}{CH_3CH{=}CHCHO} + BrMgC{\equiv}CCH_2OMgBr \rightarrow \underset{\text{XXXVI}}{CH_3CH{=}CHCHOHC{\equiv}CCH_2OH}$$

Propargyl bromide after reaction with magnesium or with zinc can be combined at the bromide end of the molecule with carbonyls or with active halogen compounds. In this way, for example, propargylmagnesium bromide with an allyl halide (XXXVII) gave 5-nonen-1-yne (114; see also 101). Carbonyl compounds to which propargylmagnesium bromide has been added to give 4-hydroxy-1-alkynes (e.g., XXXVIII) include heptanal (113), hexanal (104), acetaldehyde (98), and acetone (98). Preference for zinc instead of magnesium has been expressed (104, 112, 113; 232, p. 13). In all cases more or less of the isomeric terminal allene is produced.

$$\underset{\substack{\text{XXXVII}\\ \text{2-Hexenyl halide}}}{CH_3CH_2CH_2CH{=}CHCH_2X} + BrMgCH_2C{\equiv}CH \rightarrow \underset{\text{5-Nonen-1-yne}}{CH_3CH_2CH_2CH{=}CHCH_2CH_2C{\equiv}CH}$$

$$\underset{\text{Heptanal}}{CH_3(CH_2)_5CHO} + BrMgCH_2C{\equiv}CH \rightarrow \underset{\substack{\text{XXXVIII}\\ \text{1-Decyn-4-ol}}}{CH_3(CH_2)_5CHOHCH_2C{\equiv}CH}$$

The acetal of propargyl aldehyde forms a Grignard derivative that adds to carbonyl compounds in the normal manner (155). Methyl propiolate in liquid ammonia containing sodium amide has added to cyclohexanone (24). However, Michael addition of other ketone compounds, acting as active hydrogen compounds, to the methyl propiolate is a complication. No information on the behavior with aldehydes is available. Methyl propiolate has been used effectively in mixed Glaser coupling (Section II,L). For example, polyunsaturated ester XL was prepared as the cross product from methyl propiolate and acetylene XXXIX (43).

$$CH_3CH{=}CHC{\equiv}CC{\equiv}CH + HC{\equiv}CCOOCH_3 \xrightarrow{O_2\ (CuCl)}$$

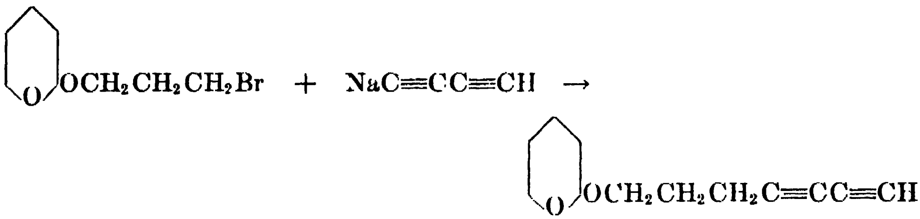
XXXIX — 2-Hepten-4,6-diyne; Methyl propiolate

$$CH_3CH{=}CHC{\equiv}CC{\equiv}CC{\equiv}CCOOCH_3$$

XL

Methyl 8-decen-2,4,6-triynoate

Allyl bromide couples readily with Grignard reagents to give terminally unsaturated chains. Peroxidic addition of hydrogen bromide affords a terminal bromide suitable for further reaction (*cf.* 286). The tetrahydropyranyl derivative of 3-bromo-1-propanol has been combined with the monosodium derivative of diacetylene to form XLI, which offered possibilities for reaction at either end of the molecule (159). Acrolein reacts with Grignard derivatives to give alkylvinylcarbinols, which can be transformed by a 1,3-shift to a primary allyl derivative (XLII). Finally, 1-heptanol is formed from the interaction of butyllithium and trimethylene oxide (XLIII), but the low yield is discouraging (250).

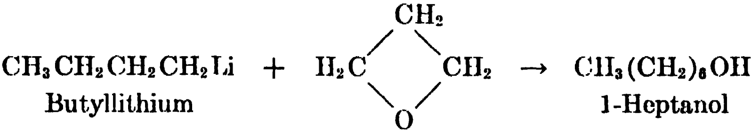


XLI

$$RMgBr + O{=}CHCH{=}CH_2 \rightarrow RCHOHCH{=}CH_2 \rightarrow \cdots \rightarrow RCH{=}CHCH_2X$$

Acrolein

XLII



Butyllithium; 1-Heptanol

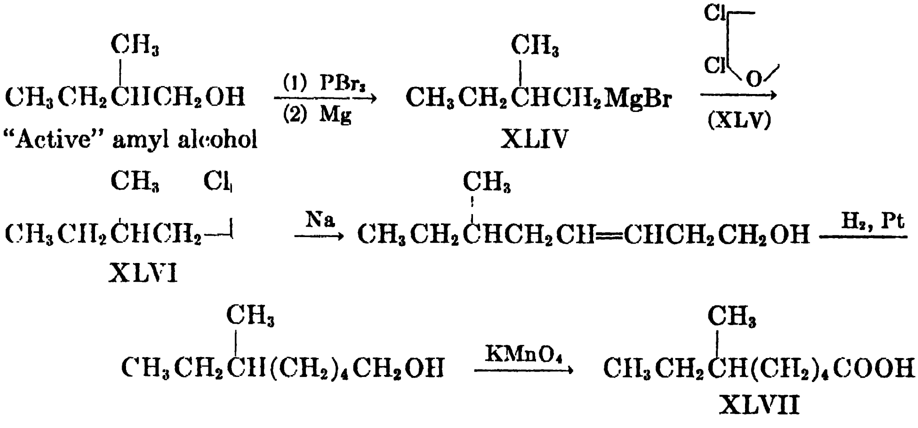
XLIII

Trimethylene oxide

E. EXTENSION OF THE CHAIN BY FOUR CARBON ATOMS

The chlorination of tetrahydrofuran as well as the addition of chlorine to 2,3-dihydrofuran (108) gives 2,3-dichlorotetrahydrofuran (XLV), which may be regarded as a cyclic analog of the α-halo ethers used in the Boord–Swallen synthesis of olefins (*cf.* 260). When this cyclic compound is used in the Boord–

Swallen synthesis, the olefinic product contains a new chain of four carbon atoms terminating in a useful hydroxyl function (*cf.* 108, 110). The accompanying formulations show how this scheme was applied to the synthesis of dextrorotatory 6-methyloctanoic acid (XLVII), one of the hydrolysis products from the antibiotic polymyxins. Grignard reagent XLIV, derived from fusel oil "active" amyl



"Active" amyl alcohol

XLIV

XLVI

XLVII

6-Methyloctanoic acid

alcohol, was coupled with 2,3-dichlorotetrahydrofuran (XLV) to give (52 per cent) a mixture of cis and trans coupling products (XLVI). Powdered sodium converted XLVI to a mixture of *cis-* and *trans*-6-methyl-3-octen-1-ols, which was first hydrogenated to 6-methyl-1-octanol and then oxidized (acid permanganate) to optically active 6-methyloctanoic acid (XLVII) (111). Although *trans*-2-alkyl-3-chlorotetrahydrofuran, e.g., XLVI, gives rise mainly to the trans olefin, the cis form gives rise to comparable amounts of the cis and trans olefins (108, 110). Accordingly, a mixture of olefins is formed. Saturation of the double bond, as in the example shown, or conversion of the double bond to a triple bond by bromination followed by dehydrobromination (101) will lead to homogeneous material.

Reaction of an excess of a Grignard reagent, e.g., isopentylmagnesium bromide, with *cis*-4-chloro-2-buten-1-ol (XLIX) adds four carbon atoms to the chain of the Grignard reagent and provides not only a reactive terminal allylic function but one entirely in the cis configuration, as in L (97). The chlorobutenol was prepared by the half-hydrogenation of 2-butyne-1,4-diol, and treatment of the

$$HOCH_2C\equiv CCH_2OH \xrightarrow[\text{catalyst}]{H_2} HOCH_2CH\overset{(cis)}{=}CHCH_2OH \xrightarrow{SOCl_2}$$

XLVIII

$$ClCH_2CH=CHCH_2OH \quad (CH_3)_2CHCH_2CH_2MgBr$$

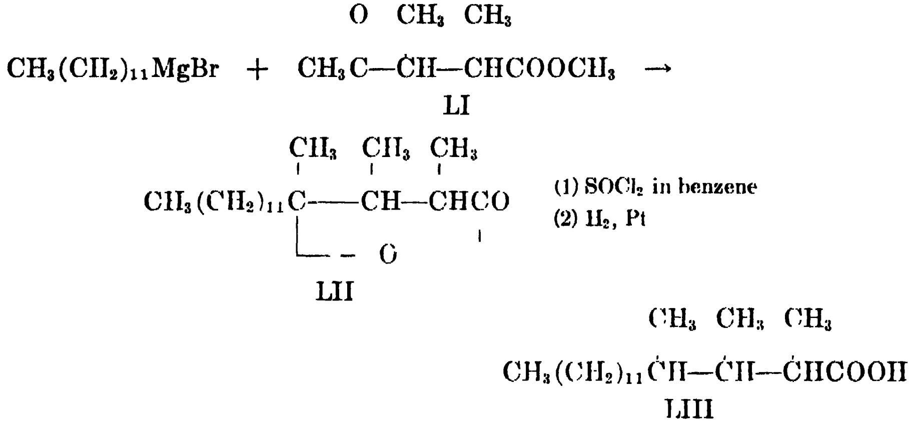
XLIX

$$(CH_3)_2CHCH_2CH_2CH_2CH\overset{(cis)}{=}CHCH_2OH$$

7-Methyl-2-octen-1-ol

cis-diol XLVIII under controlled conditions with thionyl chloride. A reagent related to 4-chloro-2-buten-1-ol (XLIX) is the tetrahydropyranyl derivative of 4-bromo-2-butyn-1-ol (129).

Another method lengthens the chain by four carbon atoms by combining a Grignard reagent with levulinic ester or a derivative. For example, dodecylmagnesium bromide with 2,3-dimethyllevulinic ester (LI) gave the γ-lactone LII. The γ-oxygen was removed by treatment first with thionyl chloride to form



$$CH_3(CH_2)_{11}MgBr + CH_3\overset{O}{C}—\overset{CH_3}{C}H—\overset{CH_3}{C}HCOOCH_3 \rightarrow$$

LI

$$CH_3(CH_2)_{11}\overset{CH_3}{C}—\overset{CH_3}{C}H—\overset{CH_3}{C}HCO \ (\text{ring } —O—) \xrightarrow[(2)\ H_2,\ Pt]{(1)\ SOCl_2 \text{ in benzene}}$$

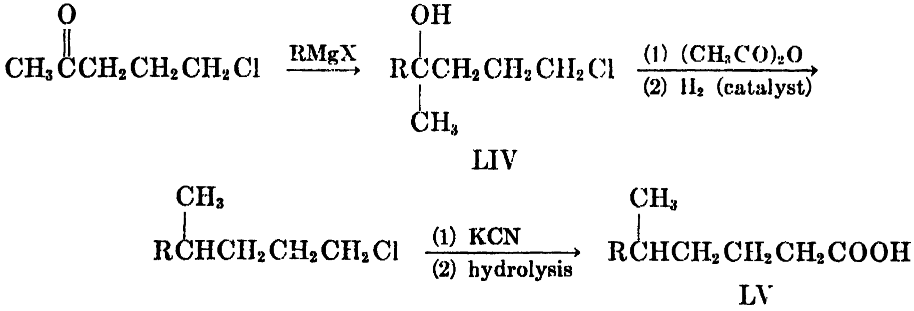
LII

$$CH_3(CH_2)_{11}\overset{CH_3}{C}H—\overset{CH_3}{C}H—\overset{CH_3}{C}HCOOH$$

LIII

2,3,4-Trimethylhexadecanoic acid

an unsaturated intermediate and then with hydrogen over platinum to saturate the double bond and to furnish 2,3,4-trimethylhexadecanoic acid (LIII) (72). When levulinic ester itself is one of the reactants, the final product is a 4-methylalkanoic acid (72, 199). Also useful is 5-chloro-2-pentanone, which with a Grignard reagent gives a tertiary alcohol (LIV). Dehydration with acetic anhydride



$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2Cl \xrightarrow{RMgX} R\underset{CH_3}{\overset{OH}{C}}CH_2CH_2CH_2Cl \xrightarrow[(2)\ H_2\ (catalyst)]{(1)\ (CH_3CO)_2O}$$

LIV

$$R\overset{CH_3}{C}HCH_2CH_2CH_2Cl \xrightarrow[(2)\ hydrolysis]{(1)\ KCN} R\overset{CH_3}{C}HCH_2CH_2CH_2COOH$$

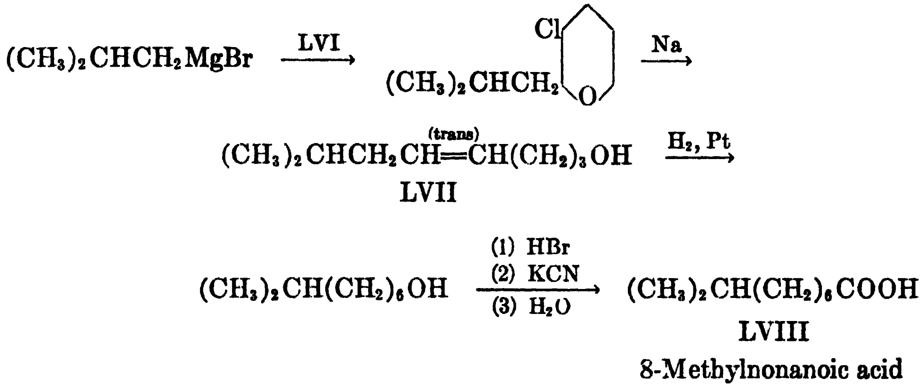
LV

and catalytic hydrogenation gives a long-chain alkyl chloride. Standard methods can convert the chlorides to a series of methyloctadecanoic acids (85). For example, when R = tridecyl, the nitrile synthesis led to 5-methylstearic acid (LV: R = tridecyl).

The addition of ethoxyvinylacetylene to aldehydes to lengthen the chain by four carbon atoms is shown in Section II,B

F. EXTENSION OF THE CHAIN BY FIVE AND SIX CARBON ATOMS

Just as 2,3-dichlorotetrahydrofuran (XLV) in the Boord–Swallen synthesis extends the chain by four carbon atoms, so 2,3-dichlorotetrahydropyran (LVI) or the 2,3-dibromo compound extends the chain by five (*cf. inter alia* 55, 108, 110, 111). The process was applied in the synthesis of 8-methylnonanoic acid (LVIII) (163), as follows: Coupling of isobutylmagnesium bromide with 2,3-dichlorotetrahydropyran gave a mixture of *cis-* and *trans*-3-chloro-2-isobutyltetrahydropyrans. Sodium powder converted the mixture to a *single* product, *trans*-7-methyl-4-octen-1-ol (LVII), which on hydrogenation and attachment of carboxylic acid in a standard nitrile synthesis gave the desired product (LVIII). If the ethylenic bond is retained so as to give unsaturated final products, the method constitutes a stereospecific mode of introducing the trans double bond (*cf.* 100, 101, 107). Two successive applications of the process, as in the conversion of butyl bromide to *trans*-4,*trans*-9-tetradecadien-1-ol (overall yield 12 per cent), adds ten carbon atoms to the chain (108).



$$(CH_3)_2CHCH_2MgBr \xrightarrow{LVI}$$

$$\xrightarrow{Na} (CH_3)_2CHCH_2\overset{(trans)}{CH{=}CH}(CH_2)_3OH \xrightarrow{H_2, Pt}$$

LVII

$$(CH_3)_2CH(CH_2)_6OH \xrightarrow[(3)\ H_2O]{(1)\ HBr \quad (2)\ KCN} (CH_3)_2CH(CH_2)_6COOH$$

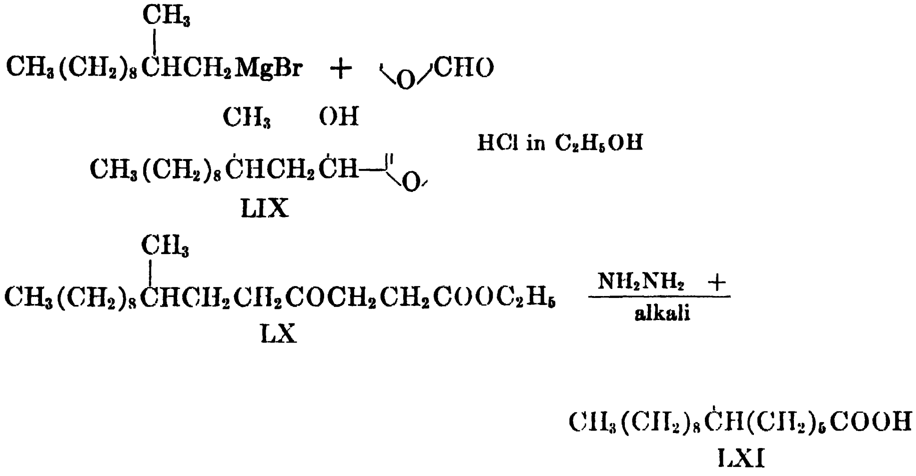
LVIII

8-Methylnonanoic acid

Condensation of an aldehyde with 3-methylglutaconic ester lengthens the aldehyde chain by attaching an unsaturated five-carbon unit bearing carboxyl groups as well as a side-chain methyl group (88, 89, 242; also *cf.* Section III,G).

A standard process by which a furfuryl alcohol in contact with mineral acid produces a γ-substituted levulinic acid has been largely neglected in the synthesis of long-chain acids. One application is in the elaboration of 2-methylundecyl bromide to 7-methylhexadecanoic acid (LXI) (290). In this synthesis 2-methylundecylmagnesium bromide with furfural gave furfuryl alcohol (LIX). The substituted levulinic ester LX was produced in 70 per cent yield when the furfuryl alcohol was treated with ethanolic hydrochloric acid. Wolff–Kishner reduction (281) completed the synthesis and gave 7-methylhexadecanoic acid (LXI).

With 4-pentyn-1-ol readily available from tetrahydrofurfuryl chloride and sodium amide, another way to extend the chain by five carbon atoms presents itself (98, 178). After protecting the hydroxyl group of the 4-pentyn-1-ol with tetrahydropyranyl, the resulting monosubstituted acetylene (LXII) is alkylated in the usual manner. With butyl bromide, for example, the product after re-



LIX

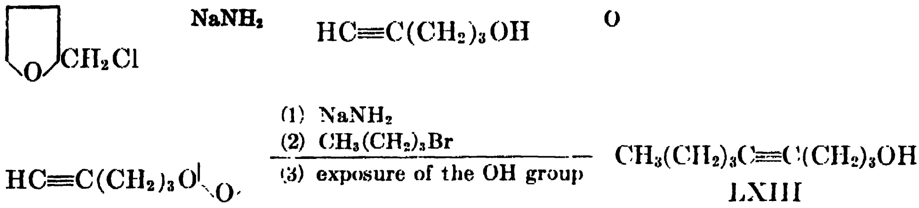
LX

$CH_3(CH_2)_8CH(CH_3)(CH_2)_6COOH$

LXI

7-Methylhexadecanoic acid

moving the blocking group is 4-nonyn-1-ol (LXIII). Analogous chain extension has been realized with other hydroxyalkylacetylenes (98, 104).



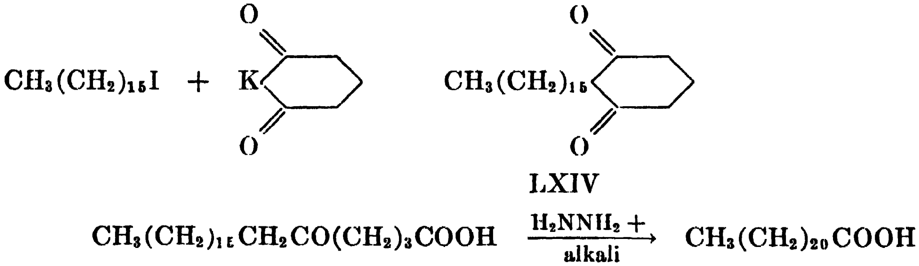
LXII

$CH_3(CH_2)_3C{\equiv}C(CH_2)_3OH$

LXIII

4-Nonyn-1-ol

A series of reactions described by Stetter and his coworkers (272) extends the chain by six carbon atoms. For example, behenic acid (LXV) was prepared in this way by alkylating potassium 1,3-cyclohexadione with hexadecyl iodide, cleaving the resulting monoalkylated diketone (LXIV) with alkali to give 5-oxo-



LXIV

$CH_3(CH_2)_{20}COOH$

LXV

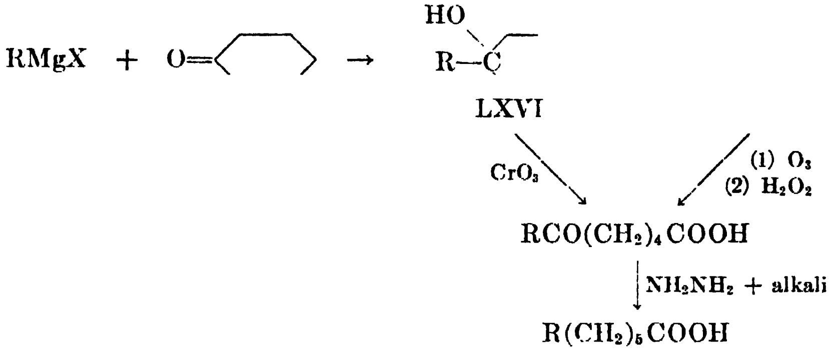
Behenic acid

behenic acid, and removing the ketonic oxygen with hydrazine and alkali. The alkylation step is not too satisfactory, inasmuch as considerable *O*-alkylation occurs.

Stetter and his associates have described many variations of this method (for Paper XII see reference 273), which, however, have been applied not so much to the synthesis of monocarboxylic acids as to that of polycarboxylic acids.

G. OXIDATION OF 1-ALKYL-1-CYCLOALKENES

Alkylmagnesium halides add to cyclic ketones to form 1-alkyl-1-hydroxycycloalkanes (e.g., LXVI). Such compounds are oxidized either directly with chromic oxide in acetic acid (127) or, after dehydration to the alkylcycloalkene,

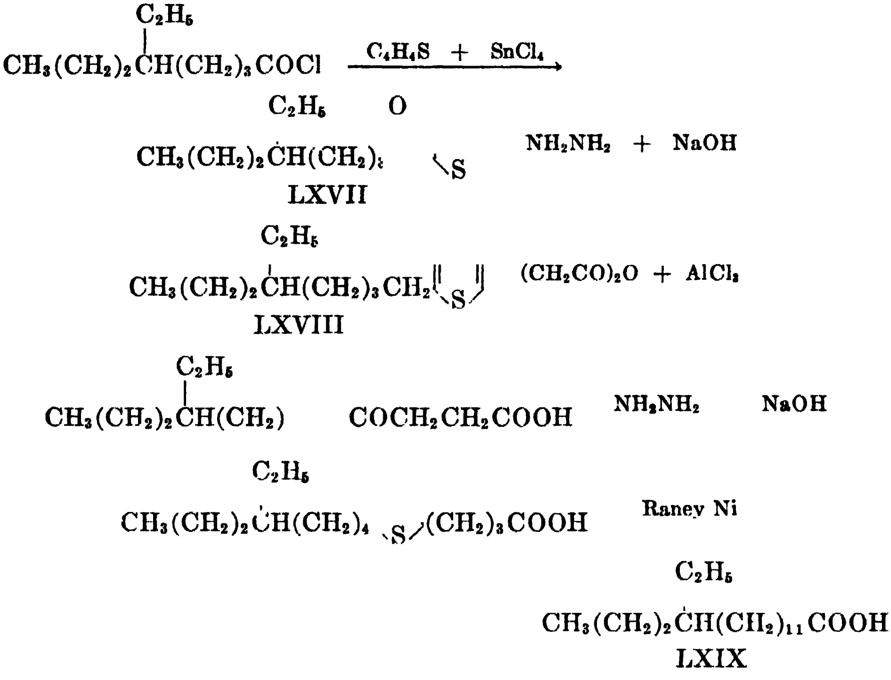


with ozone and peroxide or with chromium oxide (248) to form acyclic keto acids. Wolff-Kishner reduction completes the preparation of the long-chain acid. Application of the alcohol oxidation technique has permitted conversion of octadecyl bromide to 5-oxotetracosanoic acid and thence to tetracosanoic acid (lignoceric acid) (127), and of decyl bromide to hexadecanoic acid (185). Conversion of the tertiary alcohol from octadecylmagnesium bromide and 3,5-dimethylcyclohexanone to the acyclic keto acid failed (27). A series of "anteiso" keto acids and the corresponding "anteiso" acids were obtained by starting with 3-methylpentylmagnesium bromide and such ketones as cyclopentanone, cyclohexanone, cycloheptanone, and cyclopentadecanone (221).

In a study of the dehydration–ozonolysis method yields of cycloalkene ranged from 25 to 56 per cent, and yields of keto acid from 43 to 76 per cent (119). Examples of the dehydration–ozonolysis method would include the conversion of 3,7-dimethyloctyl bromide (tetrahydrogeranyl bromide) by reaction with cyclopentanone to 9,13-dimethyltetradecanoic acid (279), as well as the conversion of butyl bromide by reaction with cycloheptanone to undecanoic acid (119).

H. DESULFURIZATION OF ACID DERIVATIVES OF THIOPHENE

Raney nickel not only desulfurizes thiophenes but also reduces the ring unsaturation. If the carboxylic acid function is present either on the thiophene nucleus or on a substituent group, the desulfurization product is a fatty acid. Since alkyl groups, with or without a carboxylic acid group, can be easily attached to the thiophene nucleus, this process offers the possibility of preparing both normal and branched-chain acids. The overall yield is reasonable, and in only two cases was resistance noted to the desulfurization step (278). Two examples from the many reported (40, 65, 131, 168, 256, 276, 278, 299) are formulated below. The synthesis of 13-ethylhexadecanoic acid started with the acylation of thiophene with 5-ethyloctanoyl chloride in the presence of stannic chloride. Reduction of the resulting ketone (LXVII) by the Wolff–Kishner procedure gave the 2-alkylthiophene (LXVIII) in an uncomplicated manner. Acylation with succinic anhydride placed the succinyl group as expected in the 5-position, and finally Wolff–Kishner reduction and desulfurization completed the synthesis of 13-ethylhexadecanoic acid (LXIX) (26).


$CH_3(CH_2)_2CH(C_2H_5)(CH_2)_3COCl$
C_4H_4S + $SnCl_4$
$CH_3(CH_2)_2CH(C_2H_5)(CH_2)_3$
O
S
NH_2NH_2 + NaOH
$CH_3(CH_2)_2CH(C_2H_5)(CH_2)_3CH_2$
$(CH_2CO)_2O$ + $AlCl_3$
$CH_3(CH_2)_2CH(C_2H_5)(CH_2)$
$COCH_2CH_2COOH$
NH_2NH_2
NaOH
$CH_3(CH_2)_2CH(C_2H_5)(CH_2)_4$
$(CH_2)_3COOH$
Raney Ni
$CH_3(CH_2)_2CH(C_2H_5)(CH_2)_{11}COOH$

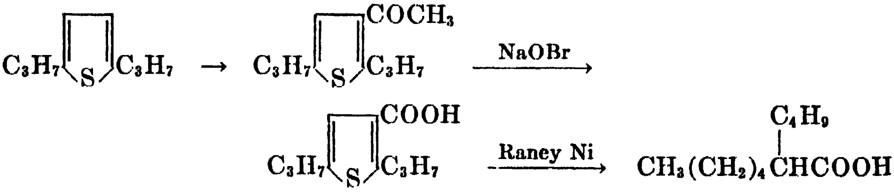
LXVII

LXVIII

LXIX

13-Ethylhexadecanoic acid

Another synthesis started with 2,5-dipropylthiophene, which by acetylation followed by haloform oxidation furnished 2,5-dipropylthiophene-3-carboxylic acid (LXX). Raney nickel converted this acid to 2-butylheptanoic acid (LXXI) (277).



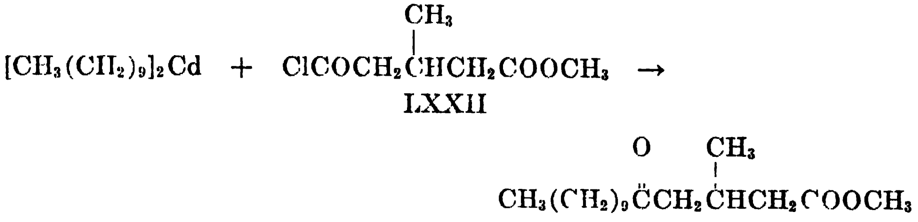
LXX

LXXI

2-Butylheptanoic acid

I. COUPLING OF AN ACID CHLORIDE WITH DIALKYLCADMIUM (255)

Grignard reagents react with cadmium chloride to form dialkylcadmium compounds, which combine readily and reliably with carbethoxy-substituted acyl chlorides to give keto esters. The keto esters are easily converted to the ketone-free acid, generally with hydrazine and alkali, but sometimes also with amalgamated zinc and hydrochloric acid. The process has found much application in the synthesis of acids (*cf.* 36, 71, 116, 121), especially branched-chain acids. For example, 3-methyl-5-oxopentadecanoic methyl ester (LXXIII) could be obtained (82 per cent yield) from didecylcadmium and acid chloride LXXII (73).



$$[CH_3(CH_2)_9]_2Cd + ClCOCH_2\overset{\overset{CH_3}{|}}{C}HCH_2COOCH_3 \rightarrow$$

LXXII

$$CH_3(CH_2)_9\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{CH_3}{|}}{C}HCH_2COOCH_3$$

LXXIII

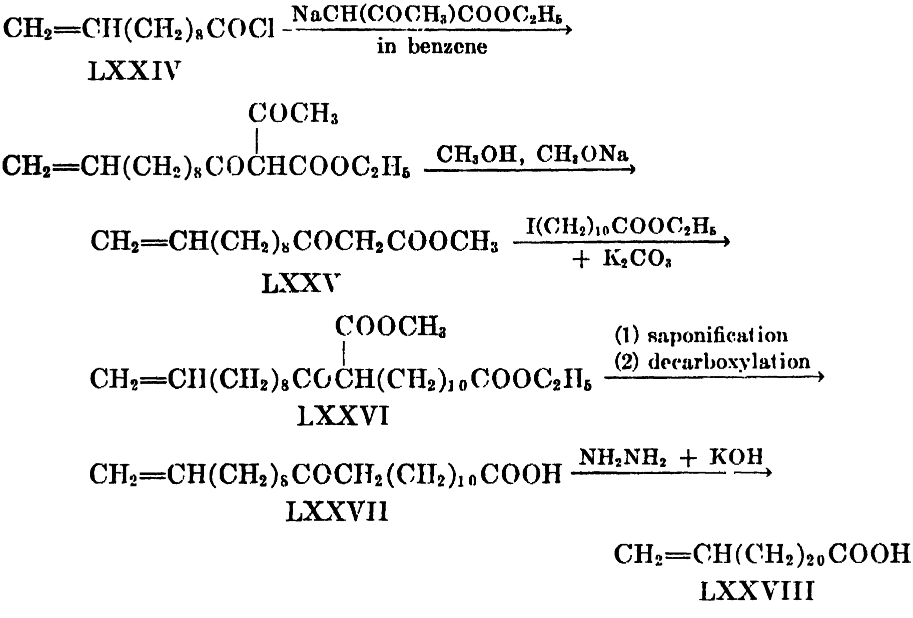
The branching can be in the dibasic acid moiety as in LXXII (*cf.* 71, 76, 77) or, as is more often the case, in the organocadmium moiety (74, 78, 79, 126, 229, 279). Unsaturation poses no problem; for example, undecenylcadmium reacts smoothly with the acid chloride from ethyl hydrogen heptanedioate to give 7-oxo-17-octadecenoic ester and, after reduction, 17-octadecenoic acid (167).

Coupling of acid chlorides with organozinc compounds to give ketones is possible (203, 209, 225, 226) but in recent years has been largely supplanted by the organocadmium method. The organozinc reaction, however, should be kept in mind as a practical alternative to the organocadmium method; in at least one case coupling with the zinc derivative was successful, while coupling with the cadmium derivative failed (247).

J. EXTENSION OF THE CHAIN BY THE ATTACHMENT OF GROUPS TO AN ACTIVE METHYLENE POSITION

1. *Methods utilizing acetoacetic ester*

Two methods of some flexibility incorporate the methylene group of malonic ester or of acetoacetic ester in the middle of a carbon chain by making the methylene group serve as the point of attachment of two larger groups. Both methods lead to intermediate keto acids, which can be reduced by standard processes to long-chain fatty acids. The first stages of the acetoacetic ester process produce long-chain β-keto esters which are themselves of some interest. The acetoacetic process is described here in terms of a specific example: namely, the conversion of undecylenic acid to 22-tricosenoic acid (271). The β-keto ester (LXXV) was prepared by acylating sodioacetoacetic ester in benzene with the acid chloride (LXXIV) of undecylenic acid, and then deacetylating by methanolysis. The β-keto ester (LXXV) was then alkylated with an ω-iodo ester, in this case 11-iodoundecanoic ester, in the presence of potassium carbonate in boiling 2-pentanone. Saponification and decarboxylation of the alkylation product (LXXVI) gave the keto acid LXXVII, which was reduced by heating with potassium hydroxide and hydrazine in triethylene glycol to 22-tricosenoic acid



$$CH_2{=}CH(CH_2)_8COCl \xrightarrow[\text{in benzene}]{NaCH(COCH_3)COOC_2H_5}$$

LXXIV

$$CH_2{=}CH(CH_2)_8CO\overset{COCH_3}{\overset{|}{C}}HCOOC_2H_5 \xrightarrow{CH_3OH,\ CH_3ONa}$$

$$CH_2{=}CH(CH_2)_8COCH_2COOCH_3 \xrightarrow[+\ K_2CO_3]{I(CH_2)_{10}COOC_2H_5}$$

LXXV

$$CH_2{=}CH(CH_2)_8CO\overset{COOCH_3}{\overset{|}{C}}H(CH_2)_{10}COOC_2H_5 \xrightarrow{\substack{\text{(1) saponification}\\ \text{(2) decarboxylation}}}$$

LXXVI

$$CH_2{=}CH(CH_2)_8COCH_2(CH_2)_{10}COOH \xrightarrow{NH_2NH_2\ +\ KOH}$$

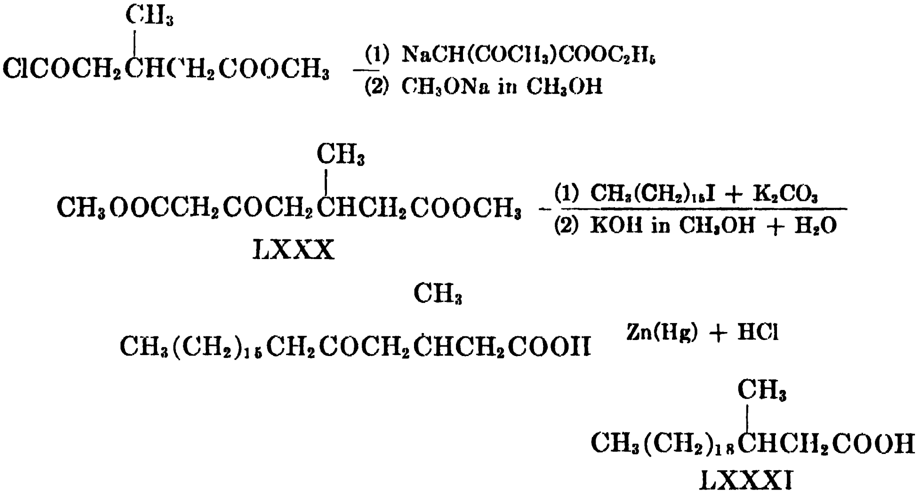
LXXVII

$$CH_2{=}CH(CH_2)_{20}COOH$$

LXXVIII

22-Tricosenoic acid

(LXXVIII). The order of constructing the chain may be reversed; that is, the acid chloride of a half-ester can be joined to acetoacetic ester to form a β-keto α,ω-dicarboxylic ester, which is then alkylated with a simple alkyl iodide. This variation was applied to the synthesis of 3-methyldocosanoic acid (LXXXI)



$$ClCOCH_2\overset{CH_3}{\overset{|}{C}}HCH_2COOCH_3 \xrightarrow{\substack{(1)\ NaCH(COCH_3)COOC_2H_5\\ (2)\ CH_3ONa\ \text{in}\ CH_3OH}}$$

$$CH_3OOCCH_2COCH_2\overset{CH_3}{\overset{|}{C}}HCH_2COOCH_3 \xrightarrow{\substack{(1)\ CH_3(CH_2)_{15}I\ +\ K_2CO_3\\ (2)\ KOH\ \text{in}\ CH_3OH\ +\ H_2O}}$$

LXXX

$$CH_3(CH_2)_{15}CH_2COCH_2\overset{CH_3}{C}HCH_2COOH \quad Zn(Hg) + HCl$$

$$CH_3(CH_2)_{18}\overset{CH_3}{\overset{|}{C}}HCH_2COOH$$

LXXXI

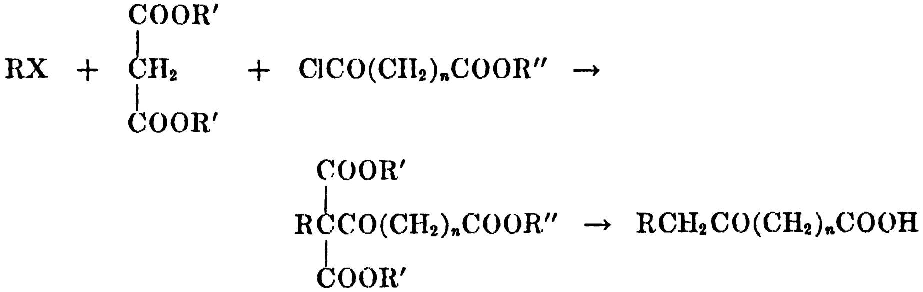
3-Methyldocosanoic acid

(268). The acid chloride of methyl hydrogen 3-methylglutarate (LXXIX) was used in the acylation of sodioacetoacetic ester. Deacetylation of the product gave the β-keto diester LXXX. Alkylation with hexadecyl iodide, saponification, decarboxylation, and Clemmensen reduction completed the synthesis.

The use of optically active methyl hydrogen 3-methylglutarate in the example just described furnished optically active products. One or the other of these procedures has been used effectively in the synthesis of a variety of fatty acids (*cf.* 14, 15, 36, 86, 130, 161, 203, 258, 269). Further examples will be found in Sections III,F and III,G.

2. *Methods utilizing malonic ester*

In the malonic ester method pictured below the methylene group of malonic ester takes over the function of the methylene group of acetoacetic ester. While in the acetoacetic ester method the characteristic and distinctive feature is clean-cut acylation and deacetylation of the ester, the essential feature in the malonic ester method is decarboxylation of the intermediate acylmalonic ester (LXXXII) without loss of the acyl group. The main difficulty lies in the fact that any attempt at ester *hydrolysis* in LXXXII preliminary to decarboxylation results in preferential hydrolytic cleavage at the acyl-to-malonate bond. The problem was solved by several devices permitting removal of the ester alkyl groups by reactions other than hydrolysis.



$$RX + CH_2(COOR')_2 + ClCO(CH_2)_nCOOR'' \rightarrow$$

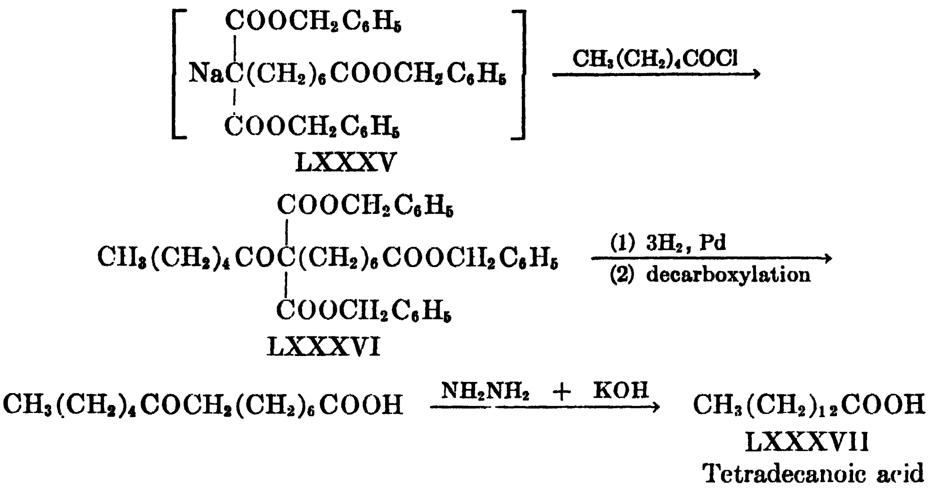
$$RC(COOR')_2CO(CH_2)_nCOOR'' \rightarrow RCH_2CO(CH_2)_nCOOH$$

LXXXII

One way to expose the acid groups in LXXXII for decarboxylation would be to have R' = benzyl and to break the benzyl-to-oxygen bond by hydrogenolysis. Formulations LXXXIII to LXXXVII for the synthesis of tetradecanoic acid illustrate how this possibility was realized (11). Alkylation of malonic ester with 7-bromoheptanoic ester (LXXXIII) gave the expected monosubstituted malonic ester (LXXXIV). The benzyl groups were introduced by ester interchange.

$$\underset{\text{LXXXIII}}{Br(CH_2)_6COOC_2H_5} \xrightarrow{NaCH(COOC_2H_5)_2}$$

$$\underset{\text{LXXXIV}}{(C_2H_5OOC)_2CH(CH_2)_6COOC_2H_5} \xrightarrow{C_6H_5CH_2ONa\ +\ C_6H_5CH_2OH}$$



$$\left[\begin{array}{l} \mathrm{COOCH_2C_6H_5} \\ \quad | \\ \mathrm{NaC(CH_2)_6COOCH_2C_6H_5} \\ \quad | \\ \mathrm{COOCH_2C_6H_5} \end{array}\right] \xrightarrow{\mathrm{CH_3(CH_2)_4COCl}}$$

LXXXV

$$\begin{array}{l} \qquad\qquad\qquad \mathrm{COOCH_2C_6H_5} \\ \qquad\qquad\qquad | \\ \mathrm{CH_3(CH_2)_4COC(CH_2)_6COOCH_2C_6H_5} \\ \qquad\qquad\qquad | \\ \qquad\qquad\qquad \mathrm{COOCH_2C_6H_5} \end{array} \xrightarrow[\text{(2) decarboxylation}]{\text{(1) } 3H_2,\ Pd}$$

LXXXVI

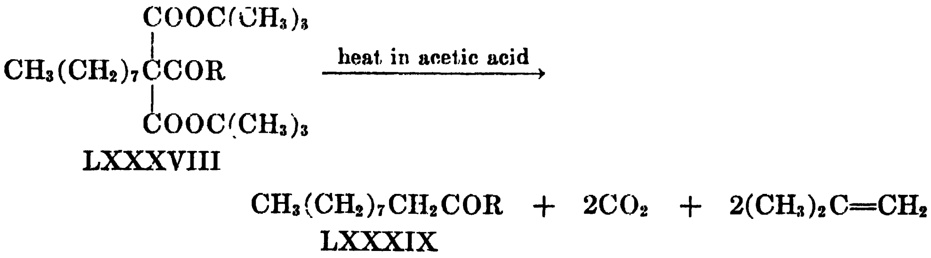
$$\mathrm{CH_3(CH_2)_4COCH_2(CH_2)_6COOH} \xrightarrow{\mathrm{NH_2NH_2\ +\ KOH}} \mathrm{CH_3(CH_2)_{12}COOH}$$

LXXXVII

Tetradecanoic acid

Treatment of LXXXIV with one mole of sodium benzyloxide and two moles of benzyl alcohol gave the sodium derivative of the tribenzyl ester (LXXXV), which was directly acylated with hexanoyl chloride. Hydrogenolysis of acylmalonic ester LXXXVI exposed the carboxyl groups, two of which were lost readily by warming in alcohol. 9-Oxotetradecanoic acid obtained in this way in 70 per cent yield from triester LXXXIV was converted by Wolff–Kishner reduction to the final product (LXXXVII). Several other fatty acids have been prepared by the debenzylation procedure (8, 9, 11, 52, 221; also *cf.* Section III,H,4).

Two alternate procedures expose the carboxyl groups without hydrolysis *and* without hydrogenolysis. The procedures accordingly are applicable to molecules containing easily hydrogenated groups. Fonken and Johnson (128) utilized di-*tert*-butyl malonate in place of diethyl malonate in standard steps leading to acylmalonate LXXXVIII. Since the *tert*-butyl ester grouping decomposes to



$$\begin{array}{l} \qquad\qquad \mathrm{COOC(CH_3)_3} \\ \qquad\qquad | \\ \mathrm{CH_3(CH_2)_7CCOR} \\ \qquad\qquad | \\ \qquad\qquad \mathrm{COOC(CH_3)_3} \end{array} \xrightarrow{\text{heat in acetic acid}}$$

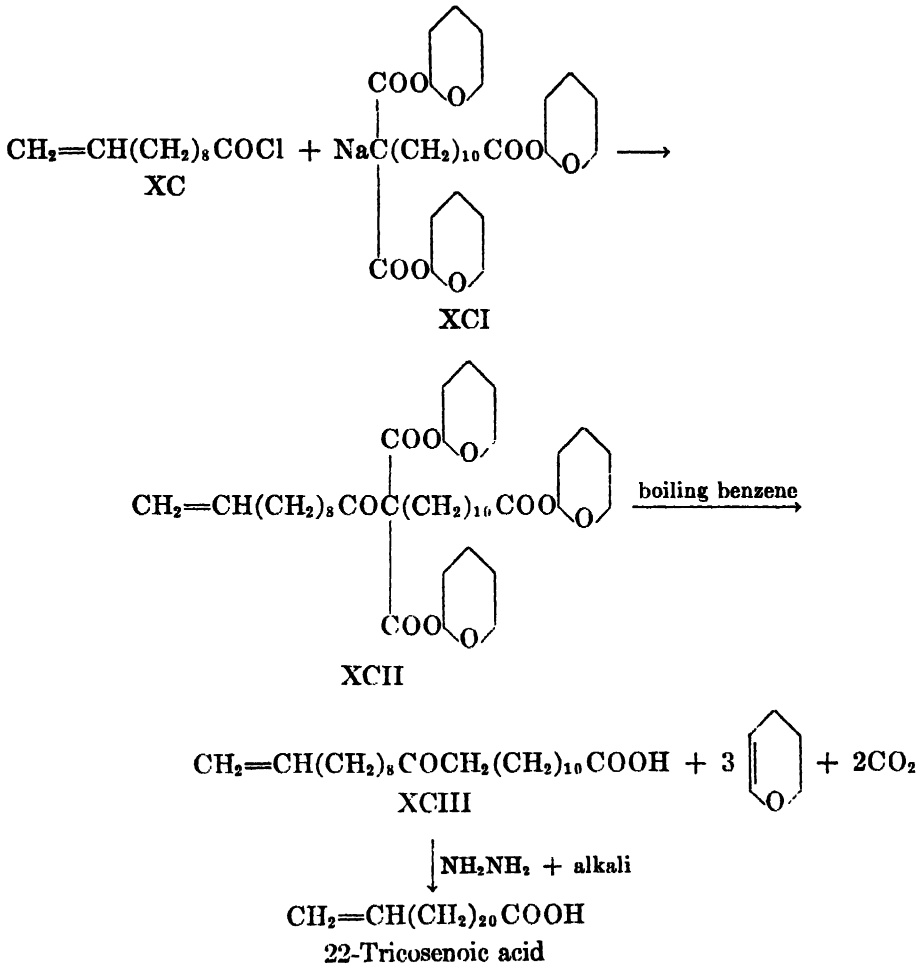
LXXXVIII

$$\mathrm{CH_3(CH_2)_7CH_2COR} + 2\mathrm{CO_2} + 2\mathrm{(CH_3)_2C{=}CH_2}$$

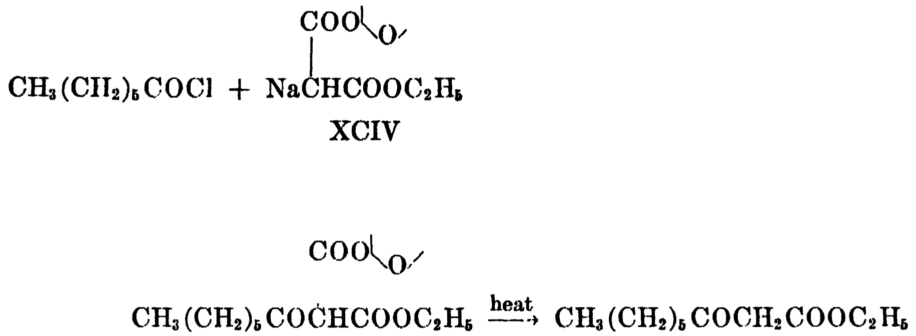
LXXXIX

acid and isobutylene on warming in acetic acid containing some *p*-toluenesulfonic acid, such treatment of LXXXVIII, by exposing labile carboxylic acid groups, permits decarboxylation to LXXXIX. Although Fonken and Johnson did not prepare acids, their method should be adaptable to this end.

Tetrahydropyranyl esters are formed by allowing carboxylic acids to react with dihydropyran in the presence of a trace of sulfuric acid. Since heating reverses the process, the ditetrahydropyranyl malonate grouping should be deesterified and then decarboxylated by heating. The use of this behavior in fatty acid work is illustrated in the following synthesis of 22-tricosenoic acid (53). Acylation of substituted malonic tetrahydropyranyl ester XCI (formed from the corresponding acid and dihydropyran) with acid chloride XC occurred normally to give acylmalonate XCII. Exposure of XCII to boiling benzene released dihydropyran and carbon dioxide to give a 75 per cent yield of the keto acid XCIII. Wolff–Kishner reduction afforded 22-tricosenoic acid. A variation makes


CH₂=CH(CH₂)₈COCl + NaC(CH₂)₁₀COO
XC
COO
COO
XCI
CH₂=CH(CH₂)₈COC(CH₂)₁₀COO
boiling benzene
XCII
CH₂=CH(CH₂)₈COCH₂(CH₂)₁₀COOH + 3 + 2CO₂
XCIII
NH₂NH₂ + alkali
CH₂=CH(CH₂)₂₀COOH
22-Tricosenoic acid

use of ethyl tetrahydropyranyl malonate (XCIV), which when acylated—for example, with heptanoyl chloride—and then heated, loses only *one* carboxyl group. The product XCV accordingly is a β-keto ester. This variation, therefore, is an alternative to the acetoacetic ester acylation-deacetylation method for preparing β-keto esters (Section II,J,1). Other applications have been reported (53, 123, 230; also *cf.* Section III,H,3).



$$CH_3(CH_2)_5COCl + Na\overset{\overset{COOC(CH_3)_3}{|}}{C}HCOOC_2H_5$$

XCIV

$$CH_3(CH_2)_5CO\overset{\overset{COOC(CH_3)_3}{|}}{C}HCOOC_2H_5 \xrightarrow{\text{heat}} CH_3(CH_2)_5COCH_2COOC_2H_5$$

K. SYNTHESIS ACCORDING TO AHMAD AND STRONG

Ahmad and Strong have described a sequence of reactions that has proved to be of considerable flexibility and general importance (6). A sodium acetylide is coupled with an α,ω-iodochloroalkane to give alkynyl chloride XCVI. This, in the nitrile synthesis, is converted to acetylenic acid XCVII. Half-hydrogenation gives the corresponding cis olefinic acid, which on isomerization over selenium

$$RC{\equiv}CH \xrightarrow[\text{(2) } I(CH_2)_nCl]{\text{(1) NaNH}_2\text{ in NH}_3} \underset{\text{XCVI}}{RC{\equiv}C(CH_2)_nCl} \xrightarrow[\text{(2) hydrolysis}]{\text{(1) KCN}}$$

$$\underset{\text{XCVII}}{RC{\equiv}C(CH_2)_nCOOH} \xrightarrow[\text{Raney Ni}]{H_2} RCH\overset{\text{(cis)}}{=}CH(CH_2)_nCOOH \xrightarrow{\text{Se}}$$

$$RCH\overset{\text{(trans)}}{=}CH(CH_2)_nCOOH$$

gives the trans acid. Variations are possible. For example, R in the above formulas can be H, so that the alkynyl chloride XCVI would be a monosubstituted acetylene. Alkylation at the acetylenic hydrogen via the sodium derivative (or via the Grignard derivative with relatively active alkylating agents (280)) gives the disubstituted acetylene XCVI, in which R is alkyl (*cf.* 31, 140, 142, 280). Application of the malonic ester synthesis to XCVI extends the chain by two carbon atoms instead of one (*cf.* 113, 142, 201, 235). Sodium acetylide with alkynyl chloride XCVI gives a diyne which can be transformed further (233). The α,ω-iodochloroalkane precursor to XCVI can be replaced with the corresponding α,ω-bromochloroalkane (*cf.* 31, 233). Also, alkylation of the acetylenic lithium derivative in dioxane instead of the sodium derivative in liquid ammonia may offer advantages (201). In at least one case, the final trans acid product was obtained directly from the acetylenic acid by reduction with sodium and liquid ammonia (164).

The Ahmad and Strong method has been used for the preparation of octadecenoic acids (5, 132, 167) and other unsaturated linear fatty acids (164, 252, 280, 298), including palmitoleic acid (252), gadoleic acid (*cis*-9-eicosenoic acid) (252), petroselenic acid (*cis*-6-octadecenoic acid) (201), linoleic acid (142, 235), and linolenic acid (112; *cf.* Section III,B). In all cases the corresponding acetylenic acids—for example, tariric acid (6-octadecynoic acid) (201)—are made available. Branched-chain fatty acids result from branched-chain starting materials, and saturated acids can be obtained by complete hydrogenation at the acetylenic acid stage or at some other stage (163, 192).

Ricinoleic acid has been synthesized by an adaptation of the Ahmad and Strong procedure (113; *cf.* Section III,H,1), as has eleostearic acid (Section III,I).

L. GLASER COUPLING OF ACETYLENES (51; ALSO 232, P. 127)

A reaction by which two molecules of monosubstituted acetylene are oxidatively combined to form a conjugated diyne, i.e., XCVIII to XCIX, is known as Glaser coupling (145). Such oxidative coupling of two *different* acetylenes gives three possible products. When one of the reactants is an ω-acetylenic ester (C) and the other is an alkylacetylene, one of the three products will be a diacetylenic monocarboxylic ester (CI). Since effective separation of the three products is possible, mixed Glaser coupling provides a general method for the synthesis of diacetylenic acids.

$$\begin{array}{ccc} 2RC{\equiv}CH & \xrightarrow{[O]} & RC{\equiv}CC{\equiv}CR \\ \text{XCVIII} & & \text{XCIX} \end{array}$$

$$CH_3CH_2CH_2C{\equiv}CH + HC{\equiv}CCH_2CH_2COOCH_3 \xrightarrow{[O]}$$

$$\begin{array}{c} CH_3CH_2CH_2C{\equiv}CC{\equiv}CCH_2CH_2COOCH_3 \\ \text{CI} \end{array}$$

Glaser coupling can be performed in any one of several ways; all, however, call for mild reaction conditions. In most of the couplings described below the oxidizing agent is oxygen, and the medium is water or aqueous methanol containing cuprous chloride, excess ammonium chloride, and either ammonia or hydrochloric acid. The mild reaction conditions permit the formation of coupling products of considerable complexity and sensitivity.

Mixed Glaser coupling has been used in syntheses of polyacetylenic esters from *Compositae*, for example, tetrahydromatricaria ester (CI) (96; also *cf.* 7, 43, 60, 95, 261), as well as for the synthesis of other more or less highly unsaturated, naturally occurring fatty acids (*cf.* Sections III,D,3, 4, and 5).

Hydroxy as well as ketone groups can be present in Glaser reactants. Examples are available in the synthesis of oenantheton (CII) (46) and cicutol (CIII) (47). Oxidation of a primary hydroxyl group in the cross-coupled product to

AGRIC. RES. INST.

$$CH_3CH_2CH_2COCH_2CH_2(CH{=}CH)_2C{\equiv}CH + HC{\equiv}CCH{=}CHCH_3 \xrightarrow{[O]} CH_3CH_2CH_2COCH_2CH_2(CH{=}CH)_2(C{\equiv}C)_2CH{=}CHCH_3$$

CII

Oenantheton

$$CH_3CH_2CH_2CH_2(CH{=}CH)_3C{\equiv}CH + HC{\equiv}C(CH_2)_3OH \xrightarrow{[O]} CH_3(CH_2)_3(CH{=}CH)_3(C{\equiv}C)_2(CH_2)_3OH$$

CIII

Cicutol

carboxyl without disruption of the molecule is possible (60, 61). For example, the trans,trans form of matricarionol (CIV), obtained by the Glaser coupling of pentenyne and hydroxypentenyne, can be converted to *trans,trans*-matricaria acid (CV).

$$CH_3CH{=}CHC{\equiv}CH + HC{\equiv}CCH{=}CHCH_2OH \rightarrow CH_3CH{=}CH(C{\equiv}C)_2CH{=}CHCH_2OH \xrightarrow{CrO_3}$$

CIV

$$CH_3CH{=}CH(C{\equiv}C)_2CH{=}CHCOOH$$

CV

M. MIXED KOLBE ELECTROLYSIS

Anodic oxidation of a mixture of two acids, RCOOH and R′COOH, gives three products: RR, R′R′, and the cross product RR′. Where one of the two reactants is the half-ester (CVI) of a dibasic acid, the cross product (CVII) is an ester of a monobasic fatty acid. Because separation of the cross product poses no insurmountable difficulty, and because the cross product in most cases can be obtained in acceptable yield, this kind of mixed Kolbe electrolysis has been found eminently suitable for the synthesis of many and diverse fatty acids. Because a 1952 review is available (288), only an abbreviated account of the method is presented below.

$$RCOOH + HOOC(CH_2)_nCOOCH_3 \xrightarrow{[O]} R(CH_2)_nCOOCH_3 + \cdots$$

CVI CVII

Most published directions call for glass vessels, platinum electrodes, and methanol containing enough sodium methoxide to neutralize a small portion of the total acids (48). Generally the methyl or ethyl half-ester is used, although some advantage has been found in the benzyl half-ester (200). A practical device for sparing the more valuable of the two reactants is to use a mixture containing three to four molar amounts of the less valuable acid for every mole of the more valuable acid. Conversion of the less expendable acid to the cross product can be materially improved in this way.

Saturated straight-chain acids react without difficulty with half-esters of saturated dibasic acids (146). Reaction with malonic half-ester, although not extensively exploited, is tantamount to homologation, and as such is an alternate to such processes as the Arndt–Eistert reaction. Branching in either reactant at the α-position tends to lower the yield; consequently, not many examples of such combinations have been reported (18, 20). Substituents such as alkyl, hydroxyl, or ketone located farther from the interacting centers create no special problems. 10-Fluorodecanoic acid and methyl hydrogen sebacate give methyl 18-fluorostearate, although in low yield (222a). Unsaturation, either ethylenic or acetylenic, no closer than the β-position causes no difficulty. Since asymmetry at positions other than alpha as well as ethylenic geometry is preserved, the mixed Kolbe method is useful for stereospecific synthesis and for establishing relationship—both optical and geometrical—between high-molecular-weight products and low-molecular-weight starting materials. Optically active methyl hydrogen 3-methylglutarate has been especially useful in inserting *C*-methyl in a single optical configuration. Optically active methyl hydrogen 3-acetoxyglutarate and 3-acetoxy-3-carbethoxypropionic acid may prove of equal value in introducing optically active hydroxyl groups (see Section III,H,5).

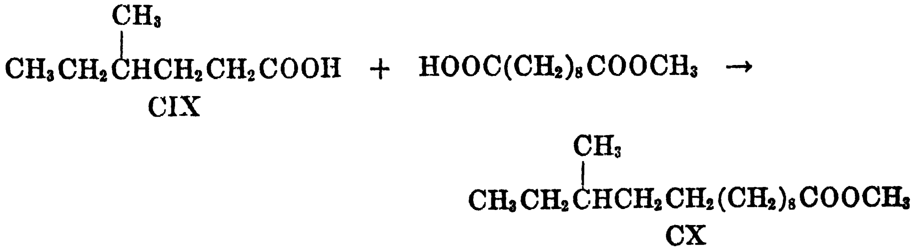
Many branched-chain acids have been prepared by mixed Kolbe electrolysis. For example, in connection with work on the wool fat acids, 12-methyltridecanoic ester (CVIII) was obtained by the anodic coupling of 4-methylpentanoic acid and ethyl hydrogen sebacate (163). A series of optically active "anteiso" acids was built up from dextrorotatory 4-methylhexanoic acid (CIX) by using the cross product from one mixed Kolbe electrolysis as the monobasic reactant in a subsequent mixed electrolysis (205). One stage, the combination of 4-methylhexanoic acid with methyl hydrogen sebacate to give methyl 12-methyltetradecanoate (CX), is formulated above. Further examples of the synthesis of

$$(CH_3)_2CHCH_2CH_2COOH + HOOC(CH_2)_8COOC_2H_5 \rightarrow$$

$$(CH_3)_2CHCH_2CH_2(CH_2)_8COOC_2H_5$$

CVIII

Ethyl 12-methyltridecanoate



$$CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_2COOH + HOOC(CH_2)_8COOCH_3 \rightarrow$$

CIX

$$CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_2(CH_2)_8COOCH_3$$

CX

Methyl 12-methyltetradecanoate

branched-chain and also cyclic acids by mixed Kolbe electrolysis will be found in Sections III,E, III,F, and III,G (also *cf.* 19, 87, 183, 196, 199, 207, 208, 210, 211, 212, 268, and 296).

Kolbe electrolysis of ethylenic or acetylenic acids occurs normally when the unsaturation is separated by at least two carbon atoms from the carboxyl group. Formation of 6-pentadecynoic acid (CXII) from valeric acid and acetylenic half-ester CXI (31), of behenolic acid (CXIII) from stearolic acid and methyl hydrogen adipate (31), and of nervonic acid (CXIV) from oleic acid and methyl hydrogen suberate (49) will illustrate the method (also *cf.* 29, 30, 48, 50). The last conversion clearly establishes cis geometry in nervonic acid.

$$CH_3(CH_2)_3COOH + HOOC(CH_2)_4C{\equiv}C(CH_2)_4COOCH_3 \xrightarrow[\text{(2) saponification}]{\text{(1) electrolysis}}$$

CXI

$$CH_3(CH_2)_7C{\equiv}C(CH_2)_4COOH$$

CXII

6-Pentadecynoic acid

$$CH_3(CH_2)_7C{\equiv}C(CH_2)_7COOH + HOOC(CH_2)_4COOCH_3 \xrightarrow[\text{(2) saponification}]{\text{(1) electrolysis}}$$

Stearolic acid

$$CH_3(CH_2)_7C{\equiv}C(CH_2)_{11}COOH$$

CXIII

Behenolic acid

$$CH_3(CH_2)_7CH\overset{\text{(cis)}}{=}CH(CH_2)_7COOH +$$

Oleic acid

$$HOOC(CH_2)_6COOCH_3 \xrightarrow[\text{(2) saponification}]{\text{(1) electrolysis}}$$

$$CH_3(CH_2)_7CH\overset{\text{(cis)}}{=}CH(CH_2)_{13}COOH$$

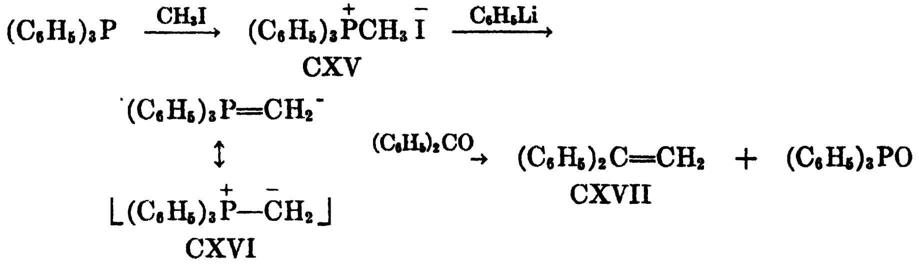
CXIV

Nervonic acid

Further flexibility is attained by utilizing a vicinal dihydroxy acid as one of the acids undergoing electrolysis, and by converting the resulting dihydroxy product to an ethylenic acid by standard methods (Section II,O,5). *trans*-Vaccenic acid was obtained in this way from hydroxylated palmitoleic acid (i.e., *threo*-9,10-dihydroxypalmitic acid) and methyl hydrogen succinate (50; see Section III,A; also *cf.* 48, 200).

N. WITTIG–GEISSLER REACTION

Wittig and Geissler (292) observed that benzophenone with methyltriphenylphosphonium iodide (CXV) that had been allowed to react with phenyllithium gave rise to 1,1-diphenylethylene (CXVII). The species CXVI reacting with the benzophenone may be described either as an alkylidene-triphenylphosphine



$$(C_6H_5)_3P \xrightarrow{CH_3I} \underset{\text{CXV}}{(C_6H_5)_3\overset{+}{P}CH_3\,\overset{-}{I}} \xrightarrow{C_6H_5Li}$$

$$\underset{\text{CXVI}}{\left[\begin{array}{c}(C_6H_5)_3P{=}CH_2\\ \updownarrow \\ (C_6H_5)_3\overset{+}{P}{-}\overset{-}{C}H_2\end{array}\right]} \xrightarrow{(C_6H_5)_2CO} \underset{\text{CXVII}}{(C_6H_5)_2C{=}CH_2} + (C_6H_5)_3PO$$

or as an ylid. The process has been found to be general. The advantage in being able to convert the carbonyl double bond in a single mild step to an ethylenic

$$\underset{\text{CXVIII}}{RCHO} + (C_6H_5)_3P{=}CHR' \rightarrow \underset{\text{CXIX}}{RCH{=}CHR'}$$

double bond, i.e., CXVIII to CXIX, is great. A disadvantage is the appearance of the product XCIX in both cis and trans forms. Although the Wittig–Geissler reaction has been extensively exploited (*cf.* 42, 44, 46, 47, 170, 171, 282, 293, 294, 295), it has not been applied directly to the synthesis of fatty acids. Nevertheless, the potentialities of the reaction for such synthesis warrant its inclusion here.

O. ETHYLENIC UNSATURATION

1. Unsaturation (α,β- and other) by elimination of hydrogen bromide

Elimination of hydrogen bromide from an alkyl bromide grouping generates a double bond. Since α-bromo acids can be obtained by standard methods, the dehydrobromination is of special interest in connection with the preparation of α,β-unsaturated acids. The method has been carefully studied, especially in connection with the "phthioic" acids (Section III,F).

The Hell-Volhard-Zelinsky bromination of acids is still the favorite way of introducing bromine into the α-position. A catalytic amount of red phosphorus can be used; however, a larger amount—or, better, one mole of phosphorus tribromide—leads to the α-bromo acid bromide, which is conveniently and directly esterified with methanol. Thionyl chloride can be used in a separate reaction before bromination to convert the acid to the acid chloride, or both steps can be combined into one by performing the bromination in thionyl chloride as solvent (249). α-Methyl acids furnish 2-bromo-2-methyl acids without difficulty. *N*-Bromosuccinimide has been used for α-bromination but is not recommended for general application (*cf.* 73).

Dehydrobromination occurs with various basic reagents with, however, varying degrees of effectiveness. For example, in the dehydrobromination of methyl 2-bromododecanoate (CXX) (71) potassium hydroxide gives mainly 2-hydroxydodecanoic acid. Potassium methoxide in methanol gives mainly the 2-methoxy ester, but potassium *tert*-butoxide in *tert*-butyl alcohol gives methyl 2-dodecenoate (CXXI) in good yield. However, the *tert*-butoxide presents complications, especially in the dehydrobromination of branched acids. Hot quinoline or pyridine is recommended as the reagent of choice for the elimination of hydrogen

$$\mathrm{CH_3(CH_2)_{10}COOH} \xrightarrow[\text{(2) esterification}]{\text{(1) } \mathrm{Br_2}} \mathrm{CH_3(CH_2)_9CHBrCOOCH_3} \longrightarrow$$

CXX

$$\mathrm{CH_3(CH_2)_8CH{=}CHCOOCH_3}$$

CXXI

Methyl 2-dodecenoate

bromide, and many alkanoic acids have been converted to 2-alkenoic acids by this bromination-dehydrobromination method (*cf. inter alia* 27, 28, 69, 70, 73, 77, 177, 215).

In connection with this preparation of 2-alkenoic acids, the possibility of α,β–β,γ tautomerism has been reëxamined. The conclusions fall in line with those reached earlier by Linstead and coworkers (144). Thus, it is generally conceded that α,β-unsaturated *acids* are relatively resistant to equilibration with alkali, and that, in any case, the α,β-position is favored when there is no substituent close to the double bond or when there is an α-methyl substituent on the double bond. Supporting illustrations would include: the absence of isomerization in 2-octadecenoic acid on relatively short exposure to boiling 10 per cent alcoholic potassium hydroxide (215); the formation of no β,γ-isomer in the dehydrohalogenation of 2-iodoöctadecanoic acid by alcoholic potassium hydroxide (176, 215); the isolation of α,β-unsaturated acid in good yield (74 per cent) on treatment of 2-bromododecanoic acid with potassium *tert*-butoxide in *tert*-butyl alcohol (71); the insensitivity of 2,5,9-trimethyl-2-decenoic acid to alcoholic potassium hydroxide (177); the absence of change in optical rotation or in ultraviolet absorption after an alcoholic potassium hydroxide solution of optically active 2,4,8-trimethyl-2-nonenoic acid is boiled for 5 hr. (177; *cf.* 28); the similar absence of change in the optical rotation of optically active 2,4-dimethyl-2-dodecenoic acid in hot alcoholic alkali (69); and the uncomplicated isolation of α,β-unsaturated products upon the dehydrobromination of a number of long-chain branched acids by quinoline or pyridine (*cf.* 27, 28, 69, 77, 177).

Stronger alkali and longer exposure may result in isomerization (*cf.* 115, 215). The isolation of mixtures of α,β- and β,γ-unsaturated acids upon the saponification of either α,β- or β,γ-unsaturated *esters* has been attributed to isomerization *before* saponification (71, 83; also 80).

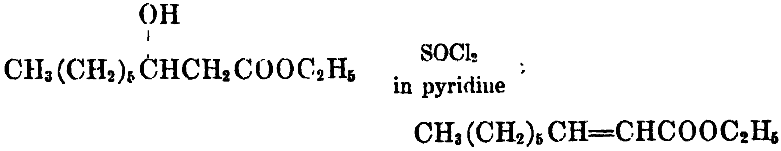
Where evidence is available it indicates that 2-alkenoic acids obtained on dehydrohalogenation have the double bond in the trans configuration (71, 215).

Halogen at positions other than alpha have been removed as hydrogen halide (83, 112, 113, 118, 126, 259). Generally, such halogen has been introduced by reaction of the corresponding alcohol with thionyl chloride, phosphorus oxychloride, phosphorus tribromide, etc. However, allylic bromination of the methyl esters of elaidic (204), oleic (204, 216), *cis*-6-octadecenoic (216), *cis*-13-docosenoic (216), 10-undecenoic (134), 12-tridecenoic (134), stearolic (216), and 13-docosynoic (216) acids with *N*-bromosuccinimide is also possible. Dehydrobromination of the bromination product from methyl elaidate with hot collidine gave a mixture from which *trans*-8,*trans*-10-octadecadienoic acid could be isolated (204). Thermal dehydrobromination gave conjugated dienes or ene-ynes (216).

2. α,β-Unsaturation by elimination of water

Dehydration of β-hydroxy esters (Section III,H,5), which are available as Reformatsky condensation products or as reduction products from β-keto esters, leads to α,β(and β,γ)-unsaturated esters. Some dehydration conditions could and probably do result in preliminary conversion of β-hydroxy to β-chloro, so that in point of fact the double bond is formed by dehydrochlorination. However, for convenience these processes will be treated here as dehydrations as long as the halogen compound is not actually isolated. Some examples are given below (also *cf.* 88, 208, 209, 242).

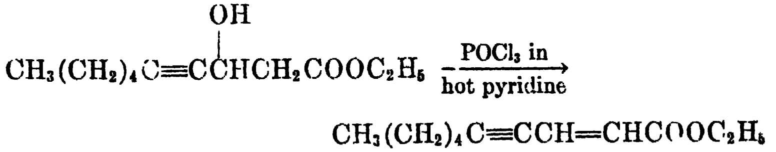
(*a*)



$$CH_3(CH_2)_5\overset{OH}{C}HCH_2COOC_2H_5 \xrightarrow[\text{in pyridine}]{SOCl_2} CH_3(CH_2)_5CH{=}CHCOOC_2H_5$$

(83)

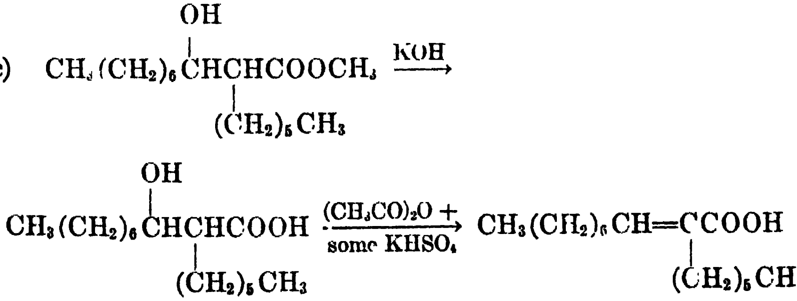
(*b*)



$$CH_3(CH_2)_4C{\equiv}C\overset{OH}{C}HCH_2COOC_2H_5 \xrightarrow[\text{hot pyridine}]{POCl_3\text{ in}} CH_3(CH_2)_4C{\equiv}CCH{=}CHCOOC_2H_5$$

(104)

(*c*)

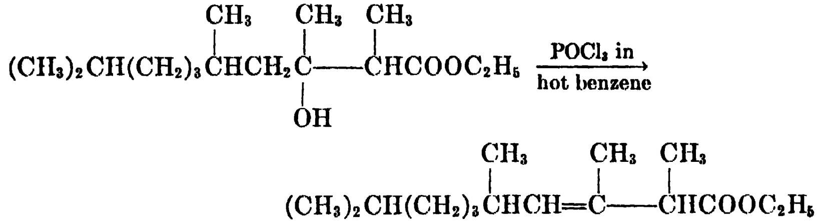


$$CH_3(CH_2)_6\overset{OH}{C}H\underset{(CH_2)_5CH_3}{C}HCOOCH_3 \xrightarrow{KOH}$$

$$CH_3(CH_2)_6\overset{OH}{C}H\underset{(CH_2)_5CH_3}{C}HCOOH \xrightarrow[\text{some }KHSO_4]{(CH_3CO)_2O\ +} CH_3(CH_2)_6CH{=}\underset{(CH_2)_5CH_3}{C}COOH$$

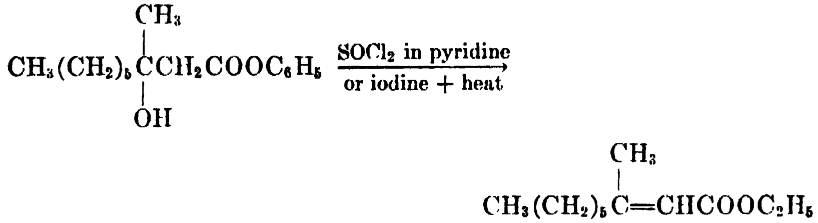
(191; also *cf.* 227)

In some cases more or less β,γ-unsaturation is observed, as follows:

(a) 

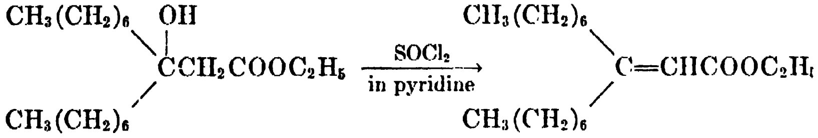
$$(CH_3)_2CH(CH_2)_3\overset{CH_3}{\overset{|}{C}}HCH_2\underset{\underset{OH}{|}}{\overset{CH_3}{\overset{|}{C}}}—\overset{CH_3}{\overset{|}{C}}HCOOC_2H_5 \xrightarrow[\text{hot benzene}]{POCl_3\text{ in}} (CH_3)_2CH(CH_2)_3\overset{CH_3}{\overset{|}{C}}HCH{=}\overset{CH_3}{\overset{|}{C}}—\overset{CH_3}{\overset{|}{C}}HCOOC_2H_5$$

CXXII

(b) 

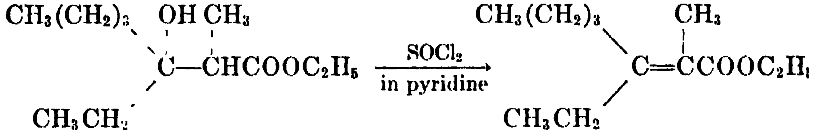
$$CH_3(CH_2)_5\underset{\underset{OH}{|}}{\overset{CH_3}{\overset{|}{C}}}CH_2COOC_6H_5 \xrightarrow[\text{or iodine + heat}]{SOCl_2\text{ in pyridine}} CH_3(CH_2)_5\overset{CH_3}{\overset{|}{C}}{=}CHCOOC_2H_5$$

CXXIII

(c) 

$$\begin{matrix}CH_3(CH_2)_6 & OH \\ & \diagdown\ | \\ & CCH_2COOC_2H_5 \\ & \diagup \\ CH_3(CH_2)_6 & \end{matrix} \xrightarrow[\text{in pyridine}]{SOCl_2} \begin{matrix}CH_3(CH_2)_6 & \\ & \diagdown \\ & C{=}CHCOOC_2H_5 \\ & \diagup \\ CH_3(CH_2)_6 & \end{matrix}$$

CXXIV

(d) 

$$\begin{matrix}CH_3(CH_2)_3 & OH\ CH_3 \\ & \diagdown\ |\quad | \\ & C—CHCOOC_2H_5 \\ & \diagup \\ CH_3CH_2 & \end{matrix} \xrightarrow[\text{in pyridine}]{SOCl_2} \begin{matrix}CH_3(CH_2)_3 & CH_3 \\ & \diagdown\quad | \\ & C{=}CCOOC_2H_5 \\ & \diagup \\ CH_3CH_2 & \end{matrix}$$

CXXV

Only a small amount of the α,β-unsaturated isomer of CXXII was obtaine (177). The α,β-unsaturated ester CXXIII was obtained mixed with two part of the β,γ-unsaturated isomer (83). Esters CXXIV and CXXV were obtainc as 58 per cent and 42 per cent mixtures with the respective β,γ-unsaturate esters (80).

β-Hydroxy esters are difficult to dehydrate with alkali. However, when tł hydroxyl group is converted to ester, e.g., to acetate, benzoate, phosphat methylsulfonate, etc., treatment with alkali does develop the α,β-unsatur tion (197).

3 *α,β-Unsaturated acids from aldehydes and ketones*

Aldehydes dissolved in pyridine containing some piperidine are condens smoothly with malonic acid to give α,β-unsaturated acids. For example, hex decanal (CXXVI) in this (Doebner) process gives 2-octadecenoic acid (17(

The major disadvantage lies in the requirement of a long-chain aldehyde. The advantages include mild reaction conditions and stereospecific formation of trans α,β-unsaturation. The yields vary widely (*cf.* 71, 100, 101, 104, 114, 174, 175, 203a). Conversion of RCH_2COOH to $RCH{=}CHCOOH$ is possible according to

$$CH_3(CH_2)_{14}CHO + CH_2(COOH)_2 \xrightarrow{\text{pyridine}} CH_3(CH_2)_{14}CH{=}CHCOOH$$

CXXVI 2-Octadecenoic acid

formulations CXXVII to CXXVIII (190). Here an even-numbered and hence readily available fatty acid such as palmitic acid is degraded by α-bromination

$$CH_3(CH_2)_{13}CHBrCOOH \xrightarrow{KOH} CH_3(CH_2)_{13}CHOHCOOH \xrightarrow{(CH_3COO)_4Pb}$$

CXXVII

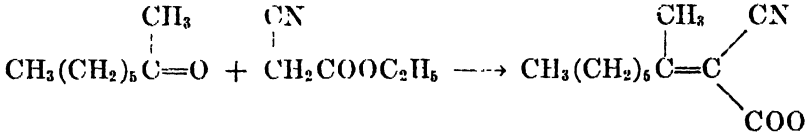
$$CH_3(CH_2)_{13}CHO \xrightarrow{CH_2(COOH)_2} CH_3(CH_2)_{13}CH{=}CHCOOH$$

CXXVIII

2-Heptadecenoic acid

(CXXVII) and alkaline hydrolysis to the 2-hydroxy acid, which with lead tetraacetate gives the odd-numbered fatty aldehyde. Doebner condensation completes the process to furnish the odd-numbered α,β-unsaturated acid (CXXVIII).

Condensation of a carbonyl compound, e.g., 2-octanone, with cyanoacetic ester to give an α,β-unsaturated cyano ester, e.g., CXXIX, has not been utilized to any great extent in the synthesis of fatty acids (9, 118).



$$CH_3(CH_2)_5\overset{\overset{CH_3}{|}}{C}{=}O + \overset{\overset{CN}{|}}{C}H_2COOC_2H_5 \longrightarrow CH_3(CH_2)_5\overset{\overset{CH_3}{|}}{C}{=}C\begin{matrix}\diagup CN \\ \diagdown COOC_2H_5\end{matrix}$$

CXXIX

Reaction of the triphenylphosphine derivative CXXX with an aliphatic aldehyde, although not reported, should give an α,β-unsaturated ester (CXXXI) without difficulty (293; also *cf.* Section II,N).

$$RCHO + (C_6H_5)_3P{=}CHCOOC_2H_5 \longrightarrow RCH{=}CHCOOC_2H_5$$

CXXX CXXXI

Addition of ethoxyacetylene to ketones, followed by treatment with aqueous sulfuric acid, generates an α,β-unsaturated ester (232, p. 82; also *cf.* Section II,C).

4. α,β-Unsaturated acids from acetylenic or ethylenic compounds

Oxidation of an allyl alcohol or an α,β-unsaturated aldehyde leads to the corresponding α,β-unsaturated acid (Section II,A). Methods for preparing α,β-unsaturated aldehydes are, accordingly, pertinent (Section II,B). Carboxylation of metal acetylides followed by half-hydrogenation to an α,β-unsaturated acid is a standard process (Section II,A and II,O,6). Carbonation of vinyllithium or of vinyl Grignard reagents gives the α,β-unsaturated acid directly (Section II,A).

Acetylenes with nickel carbonyl give α,β-unsaturated acids (179, 237). The next three sections (O,5, O,6, and O,7) should be consulted for further information on the preparation of ethylenic acids from acetylenic or ethylenic compounds.

5. *Stereospecific introduction and interconversions of ethylenic unsaturation (106)*

Control of the cis and trans nature of ethylenic unsaturation is always desirable and sometimes indispensable for the synthesis of homogeneous unsaturated acids. Some aspects of pertinent stereospecific reactions are discussed below.

The conditions of many of the chain extensions and other reactions used in fatty acid synthesis often have little if any effect on the geometry of a remote double bond. Accordingly such methods, when appropriately applied, offer stereospecific pathways to unsaturated acids As far as methods for the stereospecific generation of olefinic bonds are concerned, half-hydrogenation of a triple to a cis double bond has received by far the most extensive application (Section II,O,6). The degree of stereospecificity in reduction of the triple to the trans double bond by sodium in liquid ammonia is high, but the presence of the carboxyl group complicates the process (Section II,O,7). Reduction of γ-substituted propargyl alcohols to the trans allyl alcohol (232, p. 30) by lithium aluminum hydride should be kept in mind as potentially useful in the synthesis of fatty acids.

Trans α,β-ethylenic acids are formed efficiently and stereospecifically in the Doebner combination of aldehydes and malonic acid (Section II,O,3; also 100, 101, 104, 106, 109, 114). α,β-Unsaturated aldehydes in contact with 2 *N* sulfuric acid equilibrate so as to give almost entirely the trans form (*cf.* 100, 104, 114. 236, 263). Formulas CXXXII to CXXXIII show a useful sequence in whic this process is used. Ethyl orthoformate with acetylenic Grignard reagen CXXXII gives the acetal, which on half-hydrogenation leads to the cis ethyleni acetal. Steam distillation from aqueous acid not only hydrolyzes the acetal func

$$RC{\equiv}CMgBr \xrightarrow{HC(OC_2H_5)_3} RC{\equiv}CCH(OC_2H_5)_2 \xrightarrow[\text{catalyst}]{H_2}$$

CXXXII

$$RCH\overset{(cis)}{=}CHCH(OC_2H_5)_2 \xrightarrow{H_2O(H^+)} RCH\overset{(trans)}{=}CHCH($$

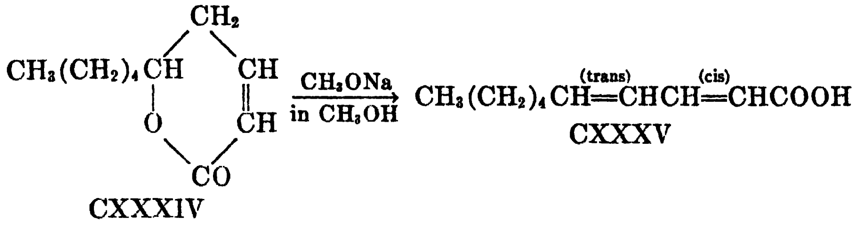
CXXXIII

tion but also isomerizes the double bond to give trans aldehyde CXXXIII.

Powdered sodium acting on either *cis*- or *trans*-2-alkyl-3-chloro(or bromo tetrahydropyran gives a trans double-bonded product in a highly stereospecif manner (Section II,F; also *cf.* 55, 107, 108, 110, 111).

Methoxide ring openings of lactones such as CXXXIV give, in a stereospeci manner, a new trans bond, as in *cis*-2,*trans*-4-decadienoic acid (CXXXV) (10 125).

A large body of information on stereospecific introduction, as well as int conversion, of ethylenic unsaturation is available in connection with work the carotenoids and on vitamin A (*cf.* Section III,G). The processes develop

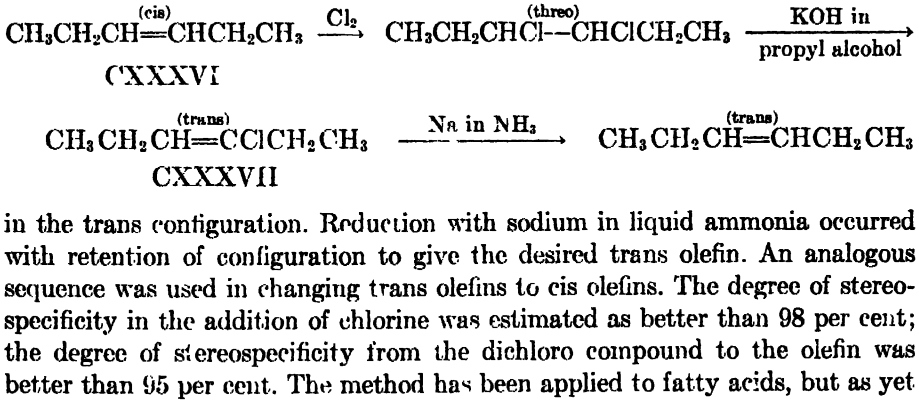


$$\xrightarrow[\text{in } CH_3OH]{CH_3ONa} CH_3(CH_2)_4CH\overset{\text{(trans)}}{=}CHCH\overset{\text{(cis)}}{=}CHCOOH$$

CXXXIV CXXXV

and used in this field are often of direct applicability to problems connected with fatty acids.

Geometrical equilibration of a double bond (with selenium, iodine, or other reagents) followed by isolation of one of the geometrical forms has been used in the synthesis of fatty acids. An alternate method of inverting the configuration of a double bond proceeds through three successive reactions of chlorination, monodehydrochlorination, and removal of the remaining chlorine by reduction with sodium and liquid ammonia (160). The process may be illustrated by the conversion of *cis*-3-hexene to *trans*-3-hexene. Chlorination of *cis*-3-hexene (CXXXVI) gave *threo*-3,4-dichlorohexane. Potassium hydroxide in propyl alcohol removed one mole of hydrogen chloride and gave vinyl chloride CXXXVII



$$CH_3CH_2CH\overset{\text{(cis)}}{=}CHCH_2CH_3 \xrightarrow{Cl_2} CH_3CH_2CHCl\overset{\text{(threo)}}{-}CHClCH_2CH_3 \xrightarrow[\text{propyl alcohol}]{\text{KOH in}}$$

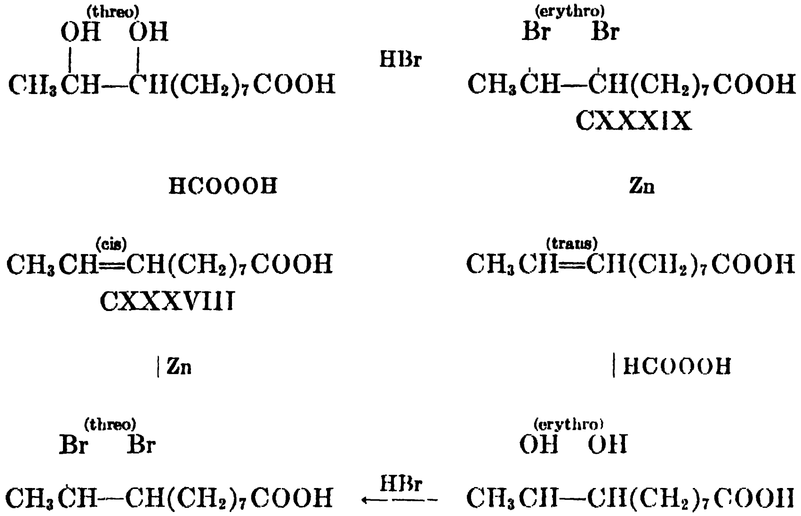
CXXXVI

$$CH_3CH_2CH\overset{\text{(trans)}}{=}CClCH_2CH_3 \xrightarrow{\text{Na in } NH_3} CH_3CH_2CH\overset{\text{(trans)}}{=}CHCH_2CH_3$$

CXXXVII

in the trans configuration. Reduction with sodium in liquid ammonia occurred with retention of configuration to give the desired trans olefin. An analogous sequence was used in changing trans olefins to cis olefins. The degree of stereospecificity in the addition of chlorine was estimated as better than 98 per cent; the degree of stereospecificity from the dichloro compound to the olefin was better than 95 per cent. The method has been applied to fatty acids, but as yet only in a preliminary fashion.

Another stereospecific interconversion of one geometric form to the other makes use of a different set of three reactions: viz., olefin hydroxylation, conversion to the dibromide, and regeneration of olefin by debromination with zinc. Under optimum conditions the stereospecificity is excellent; however, deviation from optimum conditions results in mixtures. A good example of the method may be found in the conversion of *cis*-9-undecenoic acid (CXXXVIII) to *trans*-9-undecenoic acid (CXL) and vice versa (10). Hydroxylation of *cis*-9-undecenoic acid (CXXXVIII) with per acids, e.g., performic acid, gave *threo*-9,10-dihydroxyundecanoic acid Hydrogen bromide in glacial acetic acid containing some sulfuric acid converted the threo glycol to the erythro dibromide (CXXXIX), and zinc in ethanol converted the erythro dibromide to *trans*-9-undecenoic acid (CXL). The reverse process, that is, hydroxylation of the trans acid to the erythro glycol, bromination to the threo dibromide, and debromination with zinc to *cis*-9-undecenoic acid (CXXXVIII) was also possible. The hydroxylation with per acid is completely stereospecific. The hydrobromination and debromination products are obtained homogeneous when proper reaction conditions are used.



$$\overset{\text{(threo)}}{CH_3CH(OH)\text{—}CH(OH)(CH_2)_7COOH} \xrightarrow{HBr} \overset{\text{(erythro)}}{CH_3CHBr\text{—}CHBr(CH_2)_7COOH}\ \text{CXXXIX}$$

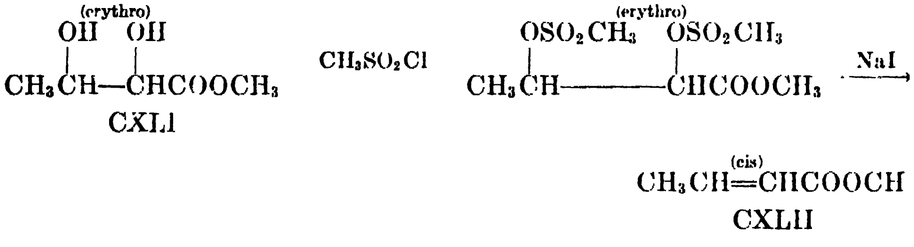
$$\overset{\text{(cis)}}{CH_3CH{=}CH(CH_2)_7COOH}\ \text{CXXXVIII} \xrightarrow{HCOOOH} \text{(threo glycol)}$$

$$\text{CXXXIX} \xrightarrow{Zn} \overset{\text{(trans)}}{CH_3CH{=}CH(CH_2)_7COOH} \xrightarrow{HCOOOH} \overset{\text{(erythro)}}{CH_3CH(OH)\text{—}CH(OH)(CH_2)_7COOH}$$

$$\overset{\text{(erythro)}}{CH_3CH(OH)\text{—}CH(OH)(CH_2)_7COOH} \xrightarrow{HBr} \overset{\text{(threo)}}{CH_3CHBr\text{—}CHBr(CH_2)_7COOH} \xrightarrow{Zn} \text{CXXXVIII}$$

Reports of several other conversions making use of these three steps have appeared (*cf.* 29, 215; also see Sections II,M, III,A, and III,H,4).

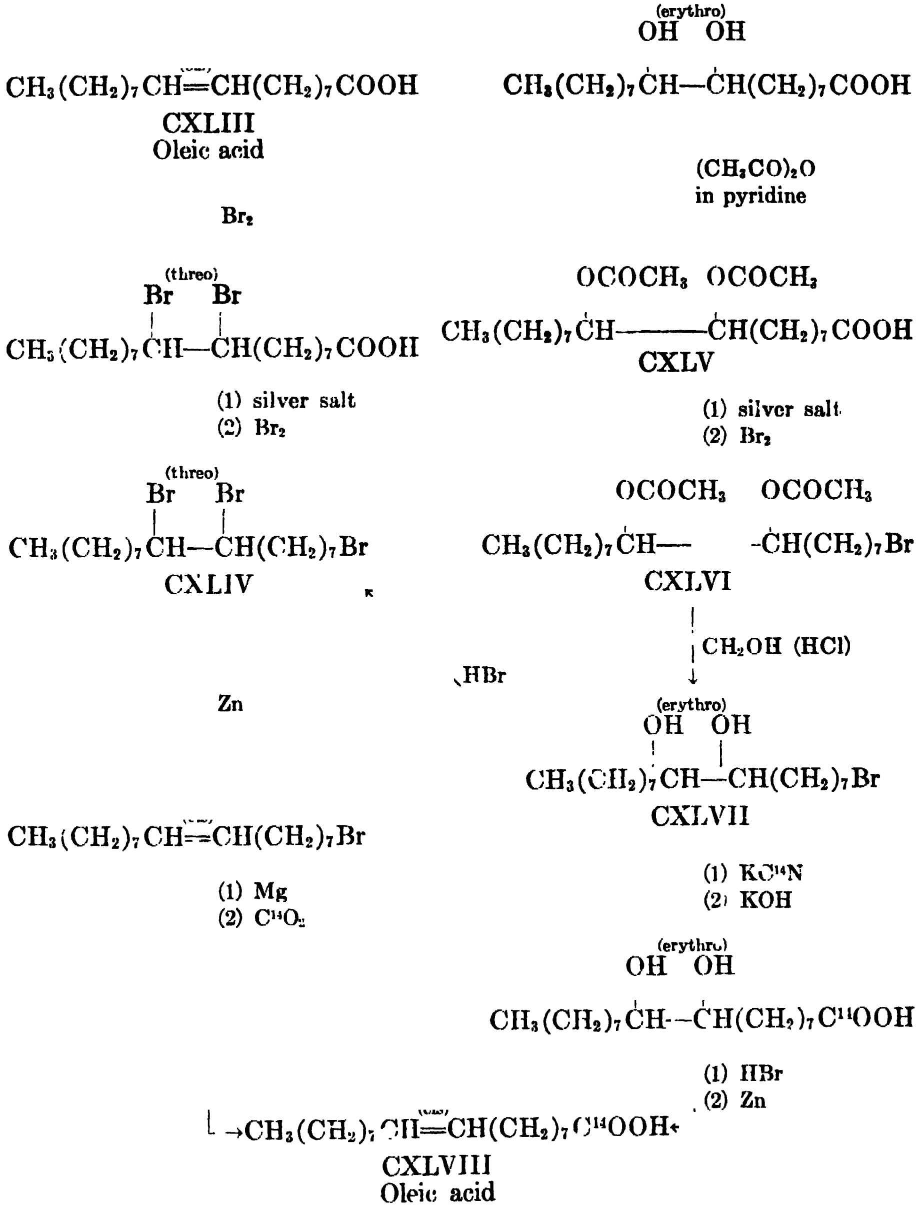
A variation of interest in that exposure of the dihydroxy acid to hydrobromination conditions is obviated, substitutes dimethanesulfonation followed by sodium iodide for the hydrobromination-debromination steps (198). For example, erythro compound CXLI with methanesulfonyl chloride was converted t the erythro dimethanesulfonate. Sodium iodide eliminated the two methan sulfonate groups to give cis compound CXLII. Whether or not this process is general applicability is not known as yet.



$$\overset{\text{(erythro)}}{CH_3CH(OH)\text{—}CH(OH)COOCH_3}\ \text{CXLI} \xrightarrow{CH_3SO_2Cl} \overset{\text{(erythro)}}{CH_3CH(OSO_2CH_3)\text{—}CH(OSO_2CH_3)COOCH_3} \xrightarrow{NaI} \overset{\text{(cis)}}{CH_3CH{=}CHCOOCH}\ \text{CXLII}$$

Vicinal glycols and dibromides have been made use of in the preparation isotopically labeled unsaturated fatty acids. For example, carboxyl-labeled ole acid was prepared by degrading *erythro*-9,10-diacetoxystearic acid (CXLV) the silver salt–bromine decarboxylation to bromide CXLVI. Ester interchan in methanolic hydrogen chloride gave the erythro dihydroxyalkyl bromi CXLVII, which by nitrile synthesis with $KC^{14}N$ gave carboxyl-labeled 9,1 dihydroxystearic acid. Regeneration of the double bond by hydrobrominati followed by debromination with zinc furnished the desired oleic acid (CXLVII

(37). Use of $KC^{13}N$ gave C^{13}-labeled oleic acid. An alternate scheme, adapted to the use of $C^{14}O_2$ instead of $KC^{14}N$, started with a stereospecific bromination of oleic acid (CXLIII) to *threo*-9,10-dibromostearic acid. Degradation of the silver



$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$
CXLIII
Oleic acid

$\xrightarrow{Br_2}$

(threo)
$CH_3(CH_2)_7\underset{}{\overset{Br}{C}}H-\overset{Br}{C}H(CH_2)_7COOH$

(1) silver salt
(2) Br_2

(threo)
$CH_3(CH_2)_7\overset{Br}{C}H-\overset{Br}{C}H(CH_2)_7Br$
CXLIV

$\xrightarrow{Zn}$

$CH_3(CH_2)_7CH{=}CH(CH_2)_7Br$

(1) Mg
(2) $C^{14}O_2$

(erythro)
$CH_3(CH_2)_7\overset{OH}{C}H-\overset{OH}{C}H(CH_2)_7COOH$

$(CH_3CO)_2O$
in pyridine

$CH_3(CH_2)_7\overset{OCOCH_3}{C}H-\overset{OCOCH_3}{C}H(CH_2)_7COOH$
CXLV

(1) silver salt
(2) Br_2

$CH_3(CH_2)_7\overset{OCOCH_3}{C}H-\overset{OCOCH_3}{C}H(CH_2)_7Br$
CXLVI

CH_3OH (HCl)

HBr

(erythro)
$CH_3(CH_2)_7\overset{OH}{C}H-\overset{OH}{C}H(CH_2)_7Br$
CXLVII

(1) $KC^{14}N$
(2) KOH

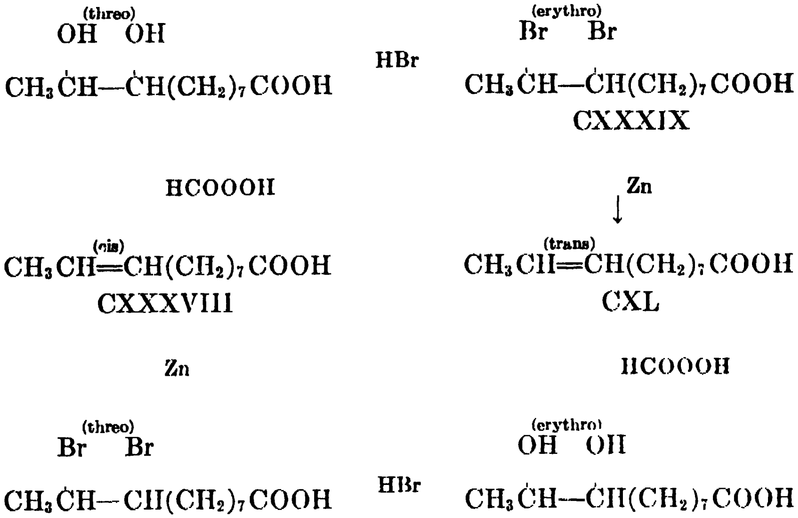
(erythro)
$CH_3(CH_2)_7\overset{OH}{C}H-\overset{OH}{C}H(CH_2)_7C^{14}OOH$

(1) HBr
(2) Zn

$\to CH_3(CH_2)_7CH{=}CH(CH_2)_7C^{14}OOH \leftarrow$
CXLVIII
Oleic acid

salt with bromine gave the threo tribromide CXLIV. Debromination with zinc, followed by Grignardation and carbonation, completed the process (166). The best features of both routes can be combined by working with the solid crystal-

cis-9-undecenoic acid (CXXXVIII) was also possible. The hydroxylation with per acid is completely stereospecific. The hydrobromination and debromination products are obtained homogeneous when proper reaction conditions are used.



$$\underset{\text{(threo)}}{\overset{OH\quad OH}{CH_3CH{-}CH(CH_2)_7COOH}} \xrightarrow{HBr} \underset{\text{CXXXIX}}{\overset{\text{(erythro)}\ Br\quad Br}{CH_3CH{-}CH(CH_2)_7COOH}}$$

$$\uparrow HCOOOH \qquad\qquad \downarrow Zn$$

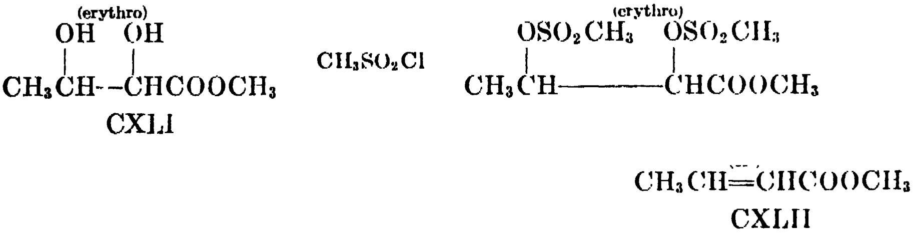
$$\underset{\text{CXXXVIII}}{\overset{\text{(cis)}}{CH_3CH{=}CH(CH_2)_7COOH}} \qquad \underset{\text{CXL}}{\overset{\text{(trans)}}{CH_3CH{=}CH(CH_2)_7COOH}}$$

$$\uparrow Zn \qquad\qquad \downarrow HCOOOH$$

$$\underset{\text{(threo)}}{\overset{Br\quad Br}{CH_3CH{-}CH(CH_2)_7COOH}} \xleftarrow{HBr} \underset{\text{(erythro)}}{\overset{OH\quad OH}{CH_3CH{-}CH(CH_2)_7COOH}}$$

Reports of several other conversions making use of these three steps have appeared (*cf.* 29, 215; also see Sections II,M, III,A, and III,H,4).

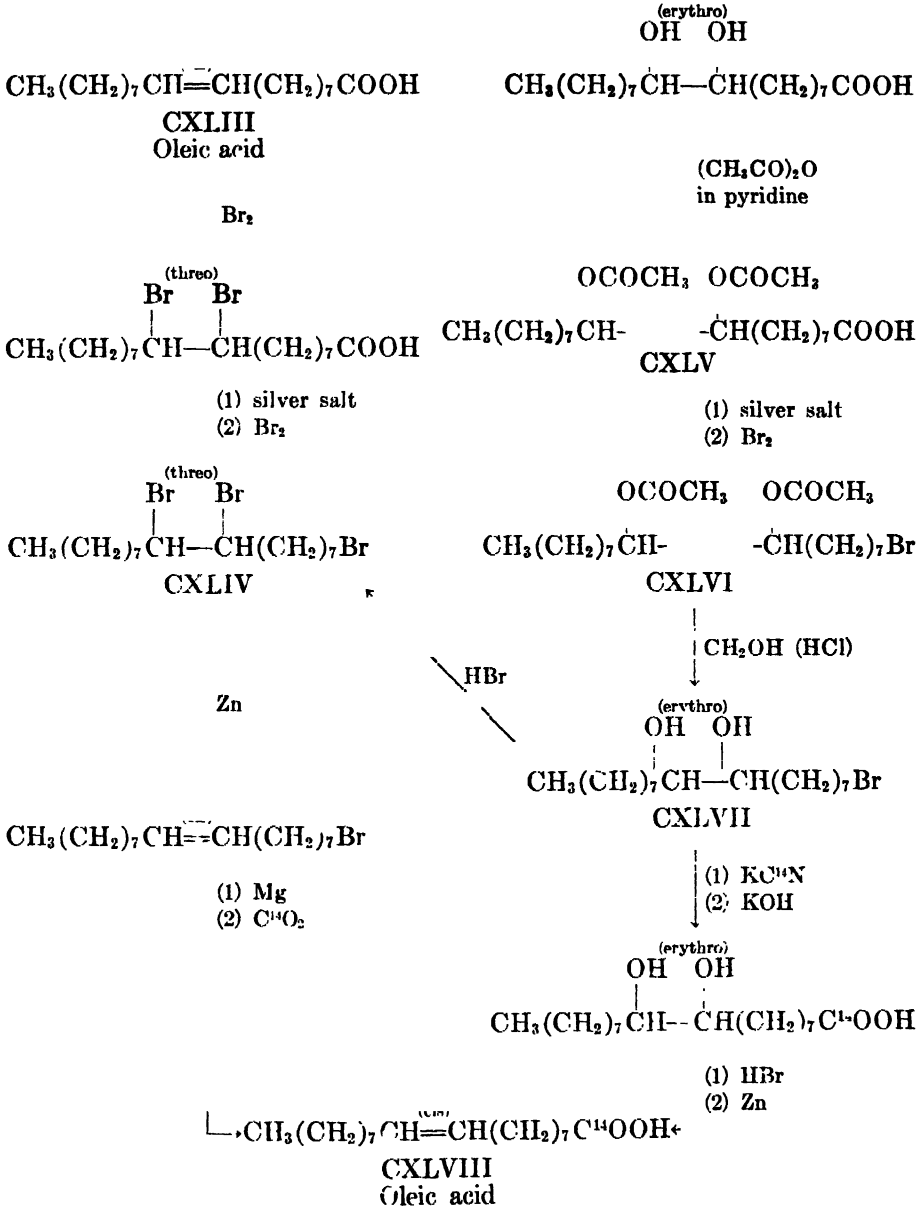
A variation of interest in that exposure of the dihydroxy acid to hydrobromination conditions is obviated, substitutes dimethanesulfonation followed by sodium iodide for the hydrobromination-debromination steps (198). For example, erythro compound CXLI with methanesulfonyl chloride was converted to the erythro dimethanesulfonate. Sodium iodide eliminated the two methanesulfonate groups to give cis compound CXLII. Whether or not this process is of general applicability is not known as yet.



$$\underset{\text{CXLI}}{\overset{\text{(erythro)}\ OH\quad OH}{CH_3CH{-}CHCOOCH_3}} \xrightarrow{CH_3SO_2Cl} \overset{\text{(erythro)}\ OSO_2CH_3\quad OSO_2CH_3}{CH_3CH{-}CHCOOCH_3} \rightarrow \underset{\text{CXLII}}{CH_3CH{=}CHCOOCH_3}$$

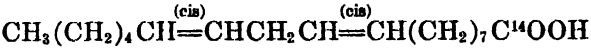
Vicinal glycols and dibromides have been made use of in the preparation of isotopically labeled unsaturated fatty acids. For example, carboxyl-labeled oleic acid was prepared by degrading *erythro*-9,10-diacetoxystearic acid (CXLV) by the silver salt–bromine decarboxylation to bromide CXLVI. Ester interchange in methanolic hydrogen chloride gave the erythro dihydroxyalkyl bromide CXLVII, which by nitrile synthesis with $KC^{14}N$ gave carboxyl-labeled 9,10-dihydroxystearic acid. Regeneration of the double bond by hydrobromination followed by debromination with zinc furnished the desired oleic acid (CXLVIII)

(37). Use of $KC^{13}N$ gave C^{13}-labeled oleic acid. An alternate scheme, adapted to the use of $C^{14}O_2$ instead of $KC^{14}N$, started with a stereospecific bromination of oleic acid (CXLIII) to *threo*-9,10-dibromostearic acid. Degradation of the silver


$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$
CXLIII
Oleic acid
Br_2
(threo)
$CH_3(CH_2)_7CH(Br)—CH(Br)(CH_2)_7COOH$
(1) silver salt
(2) Br_2
(threo)
$CH_3(CH_2)_7CH(Br)—CH(Br)(CH_2)_7Br$
CXLIV
Zn
$CH_3(CH_2)_7CH{=}CH(CH_2)_7Br$
(1) Mg
(2) $C^{14}O_2$
(erythro)
$CH_3(CH_2)_7CH(OH)—CH(OH)(CH_2)_7COOH$
$(CH_3CO)_2O$
in pyridine
$CH_3(CH_2)_7CH(OCOCH_3)—CH(OCOCH_3)(CH_2)_7COOH$
CXLV
(1) silver salt
(2) Br_2
$CH_3(CH_2)_7CH(OCOCH_3)—CH(OCOCH_3)(CH_2)_7Br$
CXLVI
CH_3OH (HCl)
HBr
(erythro)
$CH_3(CH_2)_7CH(OH)—CH(OH)(CH_2)_7Br$
CXLVII
(1) $KC^{14}N$
(2) KOH
(erythro)
$CH_3(CH_2)_7CH(OH)—CH(OH)(CH_2)_7C^{14}OOH$
(1) HBr
(2) Zn
(cis)
$CH_3(CH_2)_7CH{=}CH(CH_2)_7C^{14}OOH$
CXLVIII
Oleic acid

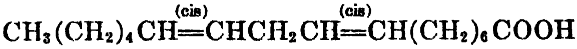
salt with bromine gave the threo tribromide CXLIV. Debromination with zinc, followed by Grignardation and carbonation, completed the process (166). The best features of both routes can be combined by working with the solid crystalline compounds from CXLV to CXLVII, and then converting dihydroxyalkyl bromide CXLVII to tribromide CXLIV. This permits the use of $C^{14}O_2$ instead of $KC^{14}N$ and the introduction of activity as late as possible (135).

A synthesis of carboxyl-labeled linoleic acid (CXLIX) makes use of stereospecific bromination and debromination with zinc (165; *cf.* Section III,B). A



$$CH_3(CH_2)_4CH\overset{(cis)}{=}CHCH_2CH\overset{(cis)}{=}CH(CH_2)_7C^{14}OOH$$

CXLIX
Linoleic acid



$$CH_3(CH_2)_4CH\overset{(cis)}{=}CHCH_2CH\overset{(cis)}{=}CH(CH_2)_6COOH$$

CL
Norlinoleic acid

synthesis of norlinoleic acid (CL) proceeds in part through common intermediates (38; *cf.* Section III,B).

6. Half-hydrogenation of acetylenic unsaturation (125a)

Catalytic half-hydrogenation of a triple bond is probably the most important general method of introducing a cis double bond. Ideal conditions for half-hydrogenation would (*a*) bring hydrogen absorption to a complete stop when one mole of hydrogen had been taken up, (*b*) give olefinic product to the exclusion of unreacted starting material and saturated material, and (*c*) furnish cis olefin to the exclusion of trans. The second feature is generally discussed under the term selectivity; the third under the term stereospecificity. Complete selectivity and complete stereospecificity are seldom if ever attained, although under proper hydrogenation conditions they may be closely approximated.

The relation of catalyst to selectivity and stereospecificity has been extensively studied. Other reaction parameters—for example, solvent or temperature—have not been as carefully studied. Systematic investigation along these lines may be rewarding. Of the possible catalysts for half-hydrogenation, platinum is clearly unsatisfactory, both selectivity and stereospecificity being low. Raney nickel or palladium in various modifications is the catalyst most frequently used.

(a) Half-hydrogenation over Raney nickel

Raney nickel is a useful but by no means an ideal catalyst for converting an acetylene to a cis olefin. The surprising report that hydrogenation of stearolic acid over Raney nickel (W-6) catalyst gave the *trans*-elaidic acid (2) is almost certainly in error (287). Some of the pertinent results on catalysis with Raney nickel are briefly summarized below.

Addition of one mole of hydrogen to 5-octynoic acid over W-5 Raney catalyst yielded (practically 100 per cent) what was regarded as essentially homogeneous *cis*-5-octenoic acid (164).

In the reduction of octadecynes to octadecenes, freshly prepared Raney nickel was found not to be particularly selective with monoacetylenes but appreciably more selective with disubstituted acetylenes. In the latter case the rates of hydrogenation before and after absorption of one mole of hydrogen differed considerably. Aged (nonpyrophoric) Raney nickel also showed large differences in the two hydrogenation rates. Raney nickel containing 10 per cent copper was found to give a fast, selective, and stereospecific reduction of octadecynes (124).

The mixtures produced when pentynes, hexynes, or octynes were hydrogenated over Raney nickel to the point at which 0.3–0.5 mole of hydrogen was absorbed gave, on fractionation, cis olefins pure to an extent of 90 per cent or better (160).

In a careful study of the hydrogenation of methyl stearolate, the catalyst used was Raney nickel which had been washed and digested to remove all or most of the free alkali and the aluminum. When exactly one mole of hydrogen had been introduced, the product consisted of methyl oleate (88.5 per cent), methyl elaidate (5.6 per cent), methyl stearate (3.7 per cent), and recovered methyl stearolate (2.1 per cent). Deuteration of methyl stearolate under similar conditions gave similar results. The alkali-free and aluminum-free catalyst gave a rate of hydrogenation of methyl stearolate after one mole had been adsorbed that was almost negligible. With 9-octadecyne, deuteration over this catalyst stopped completely at the one-mole mark and furnished *cis*-dideuterated-9-octadecene in a clean-cut manner (186).

Far less satisfactory was the behavior of a conjugated diacetylene, dimethyl 10,12-docosadiynedioate, in hydrogenation with Raney nickel at 100°C. (240). No discontinuity in rate of hydrogenation was noted until almost four moles of hydrogen had been absorbed. Analysis of the reaction mixture at intervals showed that at no time was there a significant accumulation of the conjugated ene-yne or the conjugated diene. At 25 per cent of complete hydrogenation (one mole of hydrogen absorbed) the monoacetylene, that is, dimethyl 10-docosynedioate, was present in appreciable amounts. At 75 per cent of complete hydrogenation (three moles of hydrogen absorbed) 83 per cent of the mixture was dimethyl 10-docosenedioate, of which about half was cis and half trans. This unusual behavior with respect to selectivity and stereospecificity may be the result of the 100° temperature, or less likely the effect of the conjugated diyne.

(b) Half-hydrogenation over palladium

Palladium has been used in combination with charcoal, starch, polyvinyl alcohol, calcium carbonate, barium sulfate, etc. Palladium in one or more of these forms is most widely accepted as the catalyst of choice for the hydrogenation of an acetylene to a cis olefin. However, the following brief summaries of some pertinent reports show that palladium still falls short of being the perfect catalyst.

Palladium on starch with either 1-octyne or 9-octadecyne permitted only very slow absorption of hydrogen and was only slightly specific (124). When one mole of hydrogen was added to 2-dodecynedioic acid over the same catalyst, as well as over palladium on polyvinyl alcohol, calcium carbonate, or barium sulfate, the desired *cis*-2-dodecenedioic acid was invariably accompanied by some of the overhydrogenation product, dodecanedioic acid. No trace of *trans*-2-dodecenedioic acid was observed (189). In the hydrogenation of another dibasic acid, 9-octadecynedioic acid, over 10 per cent palladium on charcoal catalyst in methanol as solvent, there was no sharp break in the hydrogenation curve, and a mixture of products was obtained at the half-hydrogenation point. However, when acid slightly less pure than the analytical material (m.p. 95–99°C. instead of 99–100°C.) was hydrogenated, absorption stopped automatically at the one-mole mark, and pure *cis*-9-octadecenedioic acid was obtained in over 90 per cent yield (140).

Hydrogenation of 2,8-dodecadiynoic acid (233), 2,6-nonadiyn-1-ol, or the acetal of 2,6-nonadiynal to the two-mole mark over palladium on calcium carbonate catalyst in ethyl acetate gave cis products, which were probably contaminated with small amounts of trans ethylenic material as well as with materials formed by overhydrogenation or nonhydrogenation of the acetylenic links (263). The rate of hydrogenation of 3-hexyn-1-ol over 5 per cent palladium on calcium carbonate catalyst in methyl acetate fell to an almost negligible value after 0.99 mole of hydrogen had been absorbed. The product was *cis*-3-hexen-1-ol contaminated with some of the *trans* isomer (264).

Some overhydrogenation was observed when palladium on barium sulfate catalyzed the absorption of one mole of hydrogen by 10-undecynoic acid (105). 9-Undecynoic acid, on absorption of 1.08 mole of hydrogen over a 5 per cent palladium on calcium carbonate catalyst in ethyl acetate, gave a product containing 92 per cent of *cis*-9-undecenoic acid. Very little if any trans product was formed, the impurities presumably consisting of starting material and undecanoic acid (10). The same catalyst with stearolic acid showed lack of both selectivity and stereospecificity (31).

The use of 5 per cent palladium on charcoal in ethanol–pyridine (4:1) as solvent has been recommended for the half-hydrogenation of 11-octadecynoic acid to *cis*-vaccenic acid. A small amount (ca. 0.1 per cent) of stearic acid was separated from the recrystallized product (88 per cent yield) (162). The beneficial effect of hydrogenation in the presence of organic base was further pointed up in the half-hydrogenation of 17-ethynyl steroids in pyridine (157), and in the half-hydrogenation of a butynylcyclopentenolone in ethyl acetate containing some quinoline (246)—both over palladium on calcium carbonate.

A palladium catalyst, prepared and used according to a recipe given by Lindlar (194), has given outstanding results. The Lindlar catalyst is 5 per cent palladium on calcium carbonate on which a small percentage of lead has been deposited. Quinoline in small proportion in the hydrogenation mixture was found to enhance selectivity and stereospecificity. In many, but not all, applications hydrogenation stopped spontaneously after the absorption of one mole of hydrogen. Some examples of the use of the Lindlar catalyst for the controlled introduction of cis unsaturation in fatty acids are given below.

Hydrogenation of stearolic acid with the Lindlar catalyst in ethyl acetate containing quinoline until no more hydrogen was absorbed gave a product in which no acetylene could be detected and in which less than 2 per cent was the saturated stearic acid (105). With the usual proportion of quinoline approximately 5 per cent of the *trans*-elaidic acid was obtained, but with slightly more than the usual proportion of quinoline this figure was reduced to 1–2 per cent (30, 31).

No stearolic and no stearic acid could be detected when the hydrogenation was interrupted at the one-mole mark; oleic acid was obtained in 74 per cent yield (after crystallization). The Lindlar catalyst gave excellent results also in the hydrogenation of 13-docosynoic acid to *cis*-13-docosenoic acid (30, 31).

Half-hydrogenation of ricinstearolic acid to ricinoleic acid over the Lindlar catalyst proceeded selectively and stereospecifically even in the absence of quinoline (113).

The selectivity with terminally unsaturated 10-undecynoic acid leaves something to be desired. Hydrogenation with the Lindlar catalyst (plus quinoline) in ethyl acetate stopped after a little more than one mole of hydrogen had been absorbed. Although no acetylenic starting material was found, 9 per cent of the saturated undecanoic acid was detected. Interruption of the hydrogenation just before hydrogenation stopped of its own accord gave some of the saturated acid as well as some acetylenic starting material (105).

Hydrogenation of methyl *trans*-2-decen-4-ynoate showed no sharp decrease in the rate of hydrogenation after one mole of hydrogen was absorbed (104). Although a mixture was obtained (selectivity low), the new double bond appeared only in the cis configuration. Absorption of two moles of hydrogen over the Lindlar catalyst by methyl 2,4-decadiynoate gave methyl *cis*-2,*cis*-4-decadienoate as the major isolated product. However, the purity of this product has been questioned (7). Other materials, the results of over- and underhydrogenation, were also obtained. Little if any trans ethylenic bond was developed (104).

Addition of two moles of hydrogen to methyl 10,12-octadecadiynoate over the Lindlar catalyst (plus quinoline) followed by fractional crystallization of the products afforded methyl *cis*-10,*cis*-12-octadecadienoate (7).

Hydrogenation of *trans*-11-octadecen-9-ynoic acid (ximenynic acid) in alcohol in the presence of the Lindlar catalyst showed no break in the hydrogenation curve after absorption of one mole of hydrogen. When the process was interrupted at the one-mole mark, *cis*-9,*trans*-11-octadecadienoic acid was obtained (149).

Introduction of one mole of hydrogen over the Lindlar catalyst to the methyl ester of *trans*-3-trideeen-5-ynoic acid gave the corresponding ester of *trans*-3,*cis*-5-tridecadienoic acid in 90 per cent yield (92).

7. *Chemical reduction of acetylenic unsaturation*

A method for reducing triple bonds to trans double bonds by treatment with sodium in liquid ammonia, although highly selective and stereospecific (*cf. inter alia* 101, 156, 264), has found little application in the synthesis of fatty acids. 5-Octynoic acid has been converted in this way to *trans*-5-octenoic acid in 85 per cent yield (164). However, attempted reduction of octadecynoic acids or of 6-dodecynedioic acid (29) failed Possibly insolubility of the sodium salts of the longer acids blocked the reaction. The reduction of octadecynes to *trans*-octadecenes, which failed at −35°C. but proceeded apparently with little difficulty at room temperature (124), suggests that higher temperatures should be tried in the reduction of the acetylenic acids.

The stereospecific reduction of a propargyl alcohol to a trans allyl alcohol by lithium aluminum hydride has not yet been applied to any considerable extent to the synthesis of fatty acids (232, p. 30).

The invalidity of the commonly accepted rule that "chemical" reduction of acetylenes gives the trans olefin has been emphasized by Rabinovitch and Looney (231). Besides the earlier observation (243) that titanous chloride and zinc in acetic acid–hydrochloric acid convert stearolic acid to oleic acid, several new cis reductions were discovered. For example, the zinc–copper couple in 95 per cent acetic acid converted tolane to *cis*-stilbene, zinc dust in alcoholic hydrogen chloride converted dideuteroacetylene to *cis*-dideuteroethylene, and the zinc–copper couple in 1*N* hydrochloric acid converted 1-deuteropropyne to the *cis*-deuteropropene. The possibility that "chemical" half-reductions giving rise to cis products are, in fact, catalytic hydrogenations has been considered.

P. ACETYLENIC UNSATURATION (173, 232)

Most syntheses of acetylenic acids proceed by the manipulation of fragments already containing the triple bond. However, some syntheses develop acetylenic unsaturation by bromination of the proper ethylene and then dehydrobromination. The dehydrobromination is effected either with potassium hydroxide or with sodium amide. Potassium hydroxide was used, for example, to convert ricinoleic acid dibromide to ricinstearolic acid (113, 147). Ethanolic potassium hydroxide converts the dibromide of 22-tricosenoic acid to 22-tricosynoic acid (271); concentrated aqueous potassium hydroxide at 150°C. converts undecylenic acid dibromide to 10-undecynoic acid (240). Potassium hydroxide at somewhat higher temperatures isomerized the latter two products to 21-tricosynoic acid and 9-undecynoic acid, respectively (10). In the same way, alkali isomerized 6,12-tridecadiynoic acid to 6,11-tridecadiynoic acid (31).

Sodium amide in liquid ammonia has been preferred by some workers for dehydrobromination because this particular kind of isomerization is not observed, and because in some cases the yields are higher. 10-Undecynoic acid (189), stearolic acid (187), and 6-octadecynoic acid (187), as well as a number of fatty acid intermediates (101, 114, 234, 263), have been prepared with sodium amide. Linoleic acid tetrabromide with sodium amide does not give 9,12-octadecadiynoic acid (187).

A study of the dehydrobromination of vicinal dibromoalkanes has shown that sodium amide under the proper conditions converts 1,2-dibromoalkanes to 1-alkynes and 2,3-dibromoalkanes to 2-alkynes with no sign of bond migration in either case. On the other hand, dehydrobromination of 3,4-dibromo and other internal vicinal dibromides by means of sodium amide occurs with bond migration (206). The homogeneity of such dehydrobromination products as ricinstearolic acid or stearolic acid, accordingly, should be carefully checked.

Q. INTRODUCTION OF BRANCHING

The presence of branched chains in several groups of natural fatty acids has stimulated considerable synthetic work on branched-chain acids (*cf.* 121). Such groups would include, on the one hand, the acids in wool wax (283; also 152, 153) terminating in the isopropyl group ("iso" series) or in the secondary butyl group ("anteiso" series) (14, 163, 205, 221) and, on the other hand, the branched-chain acids from various bacteria (23).

Simply by making use of properly branched starting materials, most of the general methods discussed before lend themselves without modification to the introduction of branching in fatty acids. Examples and references will be found scattered throughout this paper; the sections on tuberculostearic acid (III,E), "phthioic" acid (III,F), and "mycolic" acids (III,H,3) are, of course, directly pertinent. Only a sampling is given (Section III,G) of the extensive work on the branched-chain isoprenoid compounds.

Mention may be made of methods which are of utility in developing a branch at the point of juncture of two fragments. Such methods include the Reformatsky process with α-bromopropionic ester (e.g., 59, 80; also see Section III,H,5), the Reformatsky process with ketones (e.g., 59, 83), the malonic ester process with monoalkylated malonic esters (e.g., 76), and addition of organometals to ketones (e.g., 180, 192). Methyl hydrogen 3-methylglutarate, in both the racemic and the optically active forms, has been of great service in incorporating a branched methyl group by any one of several methods (*cf. inter alia* 203, 268, 269).

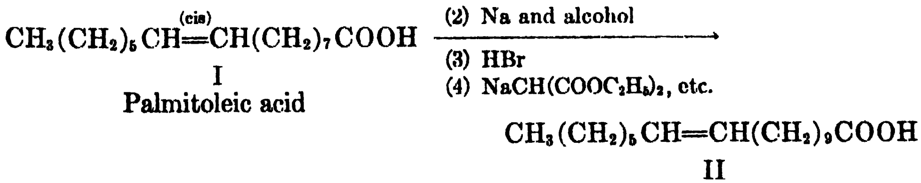
Some systematic syntheses of series of branched-chain acids deserve mention. All the monomethylstearic acids (291; also 74, 78, 85) as well as all the monomethylpalmitic acids (290) have been prepared. The 3-, 4-, 5-, 6-, and 7-monomethyldecanoic acids have been synthesized (225). Stearic acids substituted in the α-position with the entire series of normal alkyl groups from methyl to dodecyl are available (289), as is a series of 2-alkyl-3-methylnonanoic acids (120). Five long-chain acids terminating in the *tert*-butyl group have been described (259).

The contributions of Cason and his associates to the field of the synthesis and properties of branched-chain acids deserve special mention.

III. SYNTHESES OF SPECIFIC ACIDS

A. VACCENIC ACID

trans-Vaccenic acid, i.e., *trans*-11-octadecenoic acid, has been isolated from butter as well as from sheep and ox body fats. *cis*-Vaccenic acid is the principal unsaturated acid in the fats from *Lactobacillus arabinosus* and *Lactobacillus casei*. The cis acid also occurs in fat from horse brain. The original synthesis by Ahmad, Bumpus, and Strong (5) has been repeated several times (132, 167; also *cf.* 162). Alternate syntheses starting from undecylenic acid (126, 134) and from palmi-



$$\underset{\text{Palmitoleic acid}}{\underset{\text{I}}{CH_3(CH_2)_5CH\overset{(cis)}{=}CH(CH_2)_7COOH}} \xrightarrow[\substack{(3)\ HBr \\ (4)\ NaCH(COOC_2H_5)_2,\ etc.}]{\substack{(1)\ esterification \\ (2)\ Na\ and\ alcohol}}$$

$$CH_3(CH_2)_5CH{=}CH(CH_2)_9COOH$$

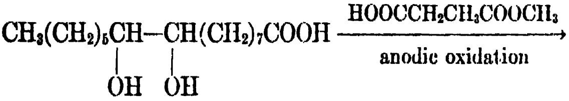
II

toleic acid have been reported. One synthesis (285) adds two carbon atoms to the carboxylic end of the sixteen-carbon palmitoleic acid (I) by Bouveault–Blanc reduction to alcohol, formation of bromide, and application of the malonate process. Although this four-step process gave a mixture of the *cis*- and *trans*-vaccenic acids (II), another scheme, by combining palmitoleic acid and methyl

$$CH_3(CH_2)_5\overset{(cis)}{CH{=}CH}(CH_2)_7COOH \xrightarrow[\text{anodic oxidation}]{HOOCCH_2CH_2COOCH_3\,(III)} CH_3(CH_2)_5CH{=}CH(CH_2)_9COOH$$

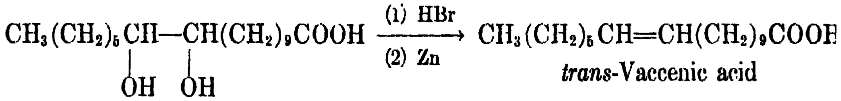
cis-Vaccenic acid

HCOOOH



$$\underset{OH}{CH_3(CH_2)_5CH}-\underset{OH}{CH}(CH_2)_7COOH \xrightarrow[\text{anodic oxidation}]{HOOCCH_2CH_2COOCH_3}$$

IV



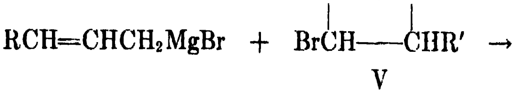
$$CH_3(CH_2)_5\underset{OH}{CH}-\underset{OH}{CH}(CH_2)_9COOH \xrightarrow[(2)\ Zn]{(1)\ HBr} CH_3(CH_2)_5CH{=}CH(CH_2)_9COOH$$

trans-Vaccenic acid

hydrogen succinate (III) in mixed Kolbe oxidation, gave pure *cis*-vaccenic acid in one step. *trans*-Vaccenic acid was obtained by cross Kolbe coupling of hydroxylated palmitoleic acid (IV) and methyl hydrogen succinate, and by regenerating the double bond by stereospecific hydrobromination and debromination (see Section II,0,5) (50).

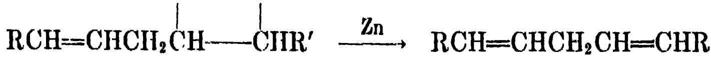
B. LINOLEIC AND LINOLENIC ACIDS (SKIPPED UNSATURATION)

Linoleic and linolenic acids (*cis*-9,*cis*-12-octadecadienoic acid and *cis*-9,*cis*-12,*cis*-15-octadecatrienoic acid, respectively), together with other naturally occurring polyunsaturated fatty acids, contain ethylenic double bonds separated by a single methylene group. The main feature in the syntheses of these acids is construction of such "methylene interrupted" or "skipped" (136) unsaturation systems. In two earlier syntheses of linoleic acid, the skipped diene system was developed by adaptation of the method of Boord and Swallen (260). In one synthesis (219) a substituted allylmagnesium bromide was coupled with an α,β-dibromo ether (V), and the resulting monoethylenic bromo ether converted to



$$RCH{=}CHCH_2MgBr + Br\overset{OCH_3}{CH}-\overset{Br}{C}HR' \rightarrow$$

V

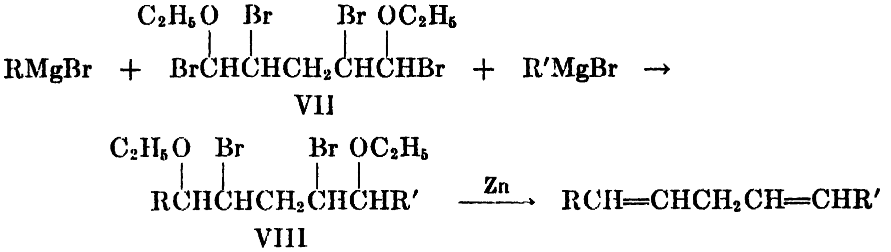


$$RCH{=}CHCH_2\overset{OCH_3}{CH}-\overset{Br}{C}HR' \xrightarrow{Zn} RCH{=}CHCH_2CH{=}CHR'$$

VI

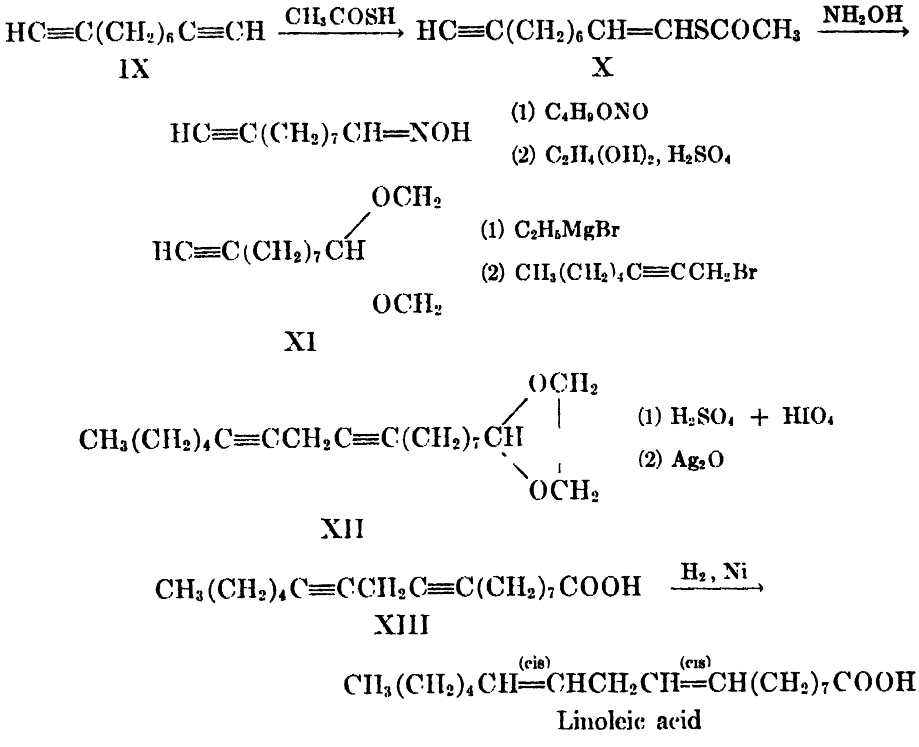
the skipped diyne (VI) with zinc. In the second synthesis (34; also *cf.* 151) two different Grignard reagents were coupled with a bis(α,β-dibromo ether) (VII).

Skipped unsaturation was developed in the *mixed* coupled product (VIII), again by reaction with zinc. Later it was found more convenient to build skipped cis diene systems by half-hydrogenating the corresponding skipped diynes, which in turn could be formed satisfactorily by coupling acetylenic Grignard derivatives either with propargyl bromides (136, 139; also *cf.* 138) or with propargyl methanesulfonates. One of the two syntheses of linoleic acid (142, 235, 287; also *cf.* 280) is outlined below (287). 1,9-Decadiyne (IX), from 1,6-dibromohexane and sodium acetylide, was combined with thioacetic acid to form the vinyl thioacetate derivative X. Hydroxylamine hydrochloride converted the thioacetate to the oxime of 9-decynal. This oxime with nitrous acid gave an aldehyde which with ethylene glycol gave the cyclic acetal XI. 1-Bromo-2-octyne with the Grignard derivative of XI and in the presence of cuprous copper gave the



$$\mathrm{RMgBr} + \underset{\text{VII}}{\mathrm{Br\overset{C_2H_5O}{\overset{|}{C}}H\overset{Br}{\overset{|}{C}}HCH_2\overset{Br}{\overset{|}{C}}H\overset{OC_2H_5}{\overset{|}{C}}HBr}} + \mathrm{R'MgBr} \rightarrow$$

$$\underset{\text{VIII}}{\mathrm{R\overset{C_2H_5O}{\overset{|}{C}}H\overset{Br}{\overset{|}{C}}HCH_2\overset{Br}{\overset{|}{C}}H\overset{OC_2H_5}{\overset{|}{C}}HR'}} \xrightarrow{Zn} \mathrm{RCH{=}CHCH_2CH{=}CHR'}$$



$$\underset{\text{IX}}{\mathrm{HC{\equiv}C(CH_2)_6C{\equiv}CH}} \xrightarrow{\mathrm{CH_3COSH}} \underset{\text{X}}{\mathrm{HC{\equiv}C(CH_2)_6CH{=}CHSCOCH_3}} \xrightarrow{\mathrm{NH_2OH}}$$

$$\mathrm{HC{\equiv}C(CH_2)_7CH{=}NOH} \quad \begin{matrix}(1)\ \mathrm{C_4H_9ONO}\\(2)\ \mathrm{C_2H_4(OH)_2,\ H_2SO_4}\end{matrix}$$

$$\underset{\text{XI}}{\mathrm{HC{\equiv}C(CH_2)_7CH\begin{matrix}\diagup\mathrm{OCH_2}\\ \diagdown\mathrm{OCH_2}\end{matrix}}} \quad \begin{matrix}(1)\ \mathrm{C_2H_5MgBr}\\(2)\ \mathrm{CH_3(CH_2)_4C{\equiv}CCH_2Br}\end{matrix}$$

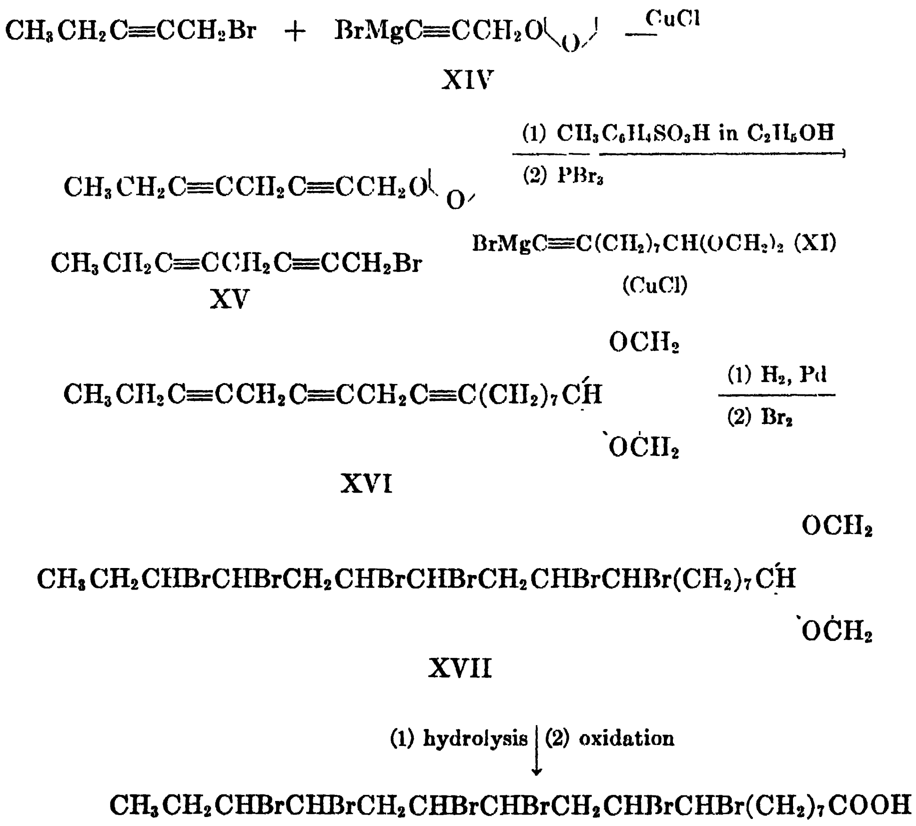
$$\underset{\text{XII}}{\mathrm{CH_3(CH_2)_4C{\equiv}CCH_2C{\equiv}C(CH_2)_7CH\begin{matrix}\diagup\mathrm{OCH_2}\\ \diagdown\mathrm{OCH_2}\end{matrix}}} \quad \begin{matrix}(1)\ \mathrm{H_2SO_4 + HIO_4}\\(2)\ \mathrm{Ag_2O}\end{matrix}$$

$$\underset{\text{XIII}}{\mathrm{CH_3(CH_2)_4C{\equiv}CCH_2C{\equiv}C(CH_2)_7COOH}} \xrightarrow{\mathrm{H_2,\ Ni}}$$

$$\underset{\text{Linoleic acid}}{\mathrm{CH_3(CH_2)_4CH\overset{(cis)}{=}CHCH_2CH\overset{(cis)}{=}CH(CH_2)_7COOH}}$$

eighteen-carbon skipped diyne compound XII. Silver oxide oxidation of the aldehyde, after removal of the protecting acetal group, gave 9,12-octadecadiynoic acid (XIII), which on half-hydrogenation afforded linoleic acid.

In a synthesis of linolenic acid (218), the skipped triene system was formed in an analogous manner by half-hydrogenation of the corresponding skipped triyne (*cf.* 137). The synthesis (218) proceeds by coupling 1-bromo-2-pentyne



$$CH_3CH_2C{\equiv}CCH_2Br + BrMgC{\equiv}CCH_2O \xrightarrow{CuCl}$$

XIV

$$CH_3CH_2C{\equiv}CCH_2C{\equiv}CCH_2O \xrightarrow[(2)\ PBr_3]{(1)\ CH_3C_6H_4SO_3H\ \text{in}\ C_2H_5OH}$$

$$CH_3CH_2C{\equiv}CCH_2C{\equiv}CCH_2Br \xrightarrow[(CuCl)]{BrMgC{\equiv}C(CH_2)_7CH(OCH_2)_2\ (XI)}$$

XV

$$CH_3CH_2C{\equiv}CCH_2C{\equiv}CCH_2C{\equiv}C(CH_2)_7CH\begin{matrix}OCH_2\\ OCH_2\end{matrix} \xrightarrow[(2)\ Br_2]{(1)\ H_2,\ Pd}$$

XVI

$$CH_3CH_2CHBrCHBrCH_2CHBrCHBrCH_2CHBrCHBr(CH_2)_7CH\begin{matrix}OCH_2\\ OCH_2\end{matrix}$$

XVII

$$\big\downarrow\ (1)\ \text{hydrolysis}\ (2)\ \text{oxidation}$$

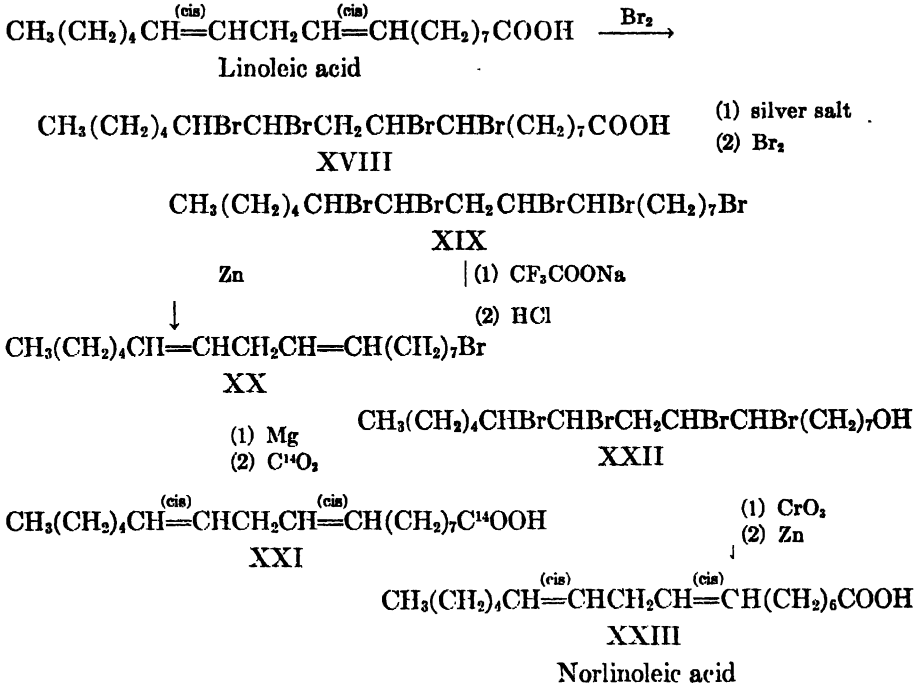
$$CH_3CH_2CHBrCHBrCH_2CHBrCHBrCH_2CHBrCHBr(CH_2)_7COOH$$

Linolenic acid hexabromide

with the acetylenic Grignard derivative XIV. Removal of the protecting tetrahydropyranyl group by treatment with alcohol containing *p*-toluenesulfonic acid was followed by conversion of the alcohol to bromide XV with phosphorus tribromide. The Grignard derivative of the acetylenic acetal XI, prepared in this work from 9-decynoic acid, was then coupled with propargyl bromide (XV) to give the eighteen-carbon skipped triyne compound XVI. Half-hydrogenation was followed by addition of bromine to give XVII. Hydrolysis of the acetal and oxidation of the exposed aldehyde grouping gave linolenic acid hexabromide, from which, by debromination with zinc, linolenic acid itself had previously been obtained.

Linoleic acid (XXI) labeled with carbon-14 in the carboxyl group has been prepared by the degradation and reconstitution of natural linoleic acid (165). Decarboxylation of linoleic acid tetrabromide (XVIII) by the action of bromine on the silver salt gave pentabromide XIX, which with zinc gave the seventeen-carbon diunsaturated bromide XX. Carbonation of the Grignard derivative of the bromide with radioactive carbon dioxide afforded labeled linoleic acid (XXI).

The same pentabromide (XIX) was used in work on the synthesis of norlinoleic acid (XXIII).



$$CH_3(CH_2)_4\overset{(cis)}{CH}{=}CHCH_2\overset{(cis)}{CH}{=}CH(CH_2)_7COOH \xrightarrow{Br_2}$$

Linoleic acid

$$CH_3(CH_2)_4CHBrCHBrCH_2CHBrCHBr(CH_2)_7COOH \quad \begin{matrix}(1)\ \text{silver salt}\\(2)\ Br_2\end{matrix}$$

XVIII

$$CH_3(CH_2)_4CHBrCHBrCH_2CHBrCHBr(CH_2)_7Br$$

XIX

Zn ↓ (1) CF_3COONa (2) HCl

$$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7Br$$

XX

$$\begin{matrix}(1)\ Mg\\(2)\ C^{14}O_2\end{matrix}$$

$$CH_3(CH_2)_4CHBrCHBrCH_2CHBrCHBr(CH_2)_7OH$$

XXII

$$CH_3(CH_2)_4\overset{(cis)}{CH}{=}CHCH_2\overset{(cis)}{CH}{=}CH(CH_2)_7C^{14}OOH$$

XXI

$$\begin{matrix}(1)\ CrO_3\\(2)\ Zn\end{matrix}$$

$$CH_3(CH_2)_4\overset{(cis)}{CH}{=}CHCH_2\overset{(cis)}{CH}{=}CH(CH_2)_6COOH$$

XXIII

Norlinoleic acid

The pentabromide was treated first with sodium trifluoroacetate and then with hydrochloric acid to effect selective conversion of primary bromide to primary alcohol, as in XXII. Oxidation gave the seventeen-carbon acid, which on debromination with zinc gave norlinoleic acid (XXIII) (38).

C. INSECTICIDAL FATTY ACID AMIDES

Herculin, an insecticidal principle from Southern prickly ash, is the isobutyl amide of a twelve-carbon unsaturated straight-chain acid. The original suggestion that herculin was *N*-isobutyl-2,8-dodecadienamide led to the synthesis of all four possible geometrically isomeric forms of XXIV, none of which, however, proved to be identical with herculin. Reinvestigation led to a revised structure (XXV) (102) and a new name, neoherculin, for the insecticidal material. The revised structure has not yet been corroborated by synthesis. In related work, synthesis of the four stereoisomers of *N*-isobutyl-2,6-decadienamide (XXVI) (101, 234) proved that this structure could not be correct for pellitorine, an insecticide from *Anacyclus pyrethrum*. Later it was shown that a major component of "pellitorine," which was not homogeneous, was the isobutyl amide of *trans*-2,*trans*-4-decadienoic acid (XXVII) (103). During the course of the work,

$CH_3(CH_2)_2CH{=}CH(CH_2)_4CH{=}CHCONHCH_2CH(CH_3)_2$

XXIV

N-Isobutyl-2,8-dodecadienamide

$CH_3CH{=}CHCH{=}CHCH{=}CHCH_2CH_2CH{=}CHCONHCH_2CH(CH_3)_2$

XXV

Neoherculin

$CH_3CH_2CH_2CH{=}CHCH_2CH_2CH{=}CHCONHCH_2CH(CH_3)_2$

XXVI

N-Isobutyl-2,6-decadienamide

$CH_3(CH_2)_4CH{=}CHCH{=}CHCONHCH_2CH(CH_3)_2$

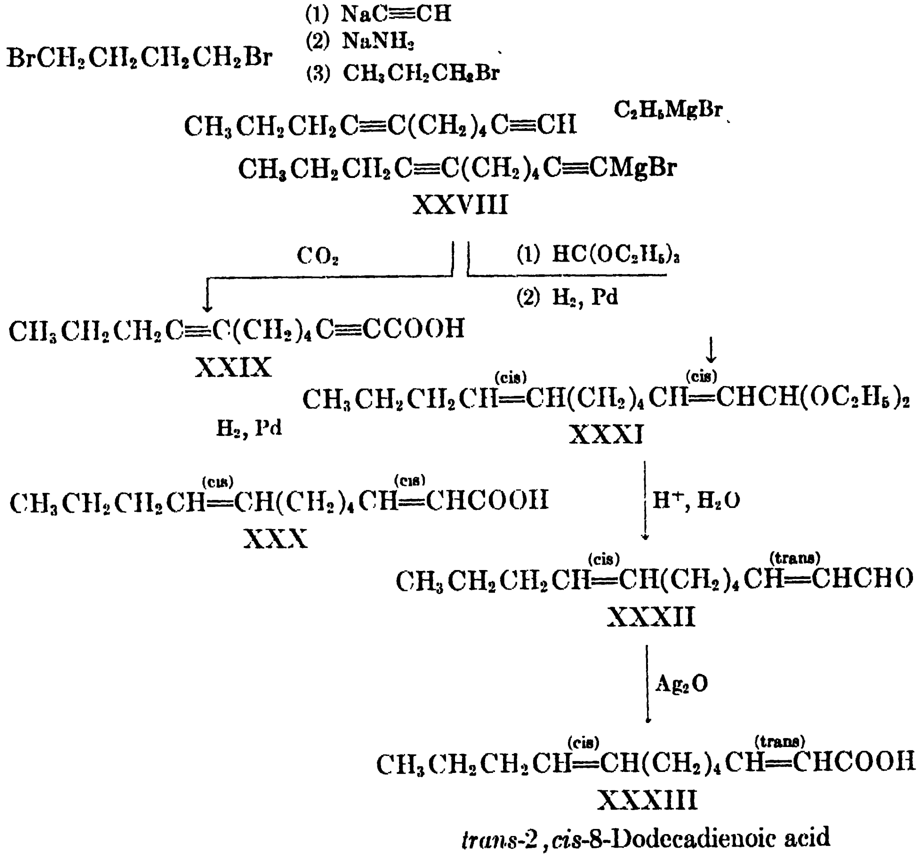
XXVII

N-Isobutyl-2,4-decadienamide

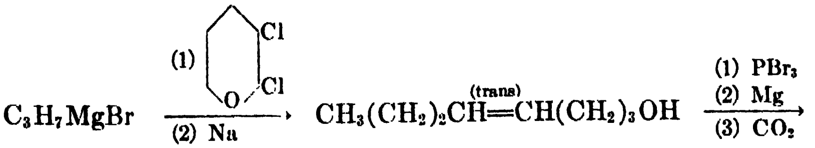
all four geometrical isomers of 2,4-decadienoic acid (*cf.* Section III,J) were prepared (104, 174).

To illustrate some of the reactions employed for these syntheses and, more important, to show how geometry at the double bond is controlled, the steps in the preparation of the four 2,8-dodecadienoic acids are discussed below in some detail. The acids with $\Delta^{8,9}$ cis were prepared (233, 236) by way of 1,7-undecadiyne, which was prepared from 1,4-dibromobutane by combination with sodium acetylide and then monoalkylation of the resulting 1,7-octadiyne with propyl iodide. Carbonation of the Grignard derivative of 1,7-undecadiyne XXVIII gave 2,8-dodecadiynoic acid (XXIX), which on half-hydrogenation over palladium on calcium carbonate gave *cis*-2,*cis*-8-dodecadienoic acid (XXX). The same Grignard derivative (XXVIII) with ethyl orthoformate led to the expected acetal, which on half-hydrogenation gave the diolefinic (cis,cis) acetal XXXI. Steam distillation from aqueous oxalic acid not only exposed the free aldehyde but also isomerized the cis α,β double bond in a stereospecific manner to trans. Oxidation of *trans*-2,*cis*-8 aldehyde XXXII with silver nitrate in aqueous sodium hydroxide solution furnished the desired *trans*-2,*cis*-8-dodecadienoic acid (XXXIII).

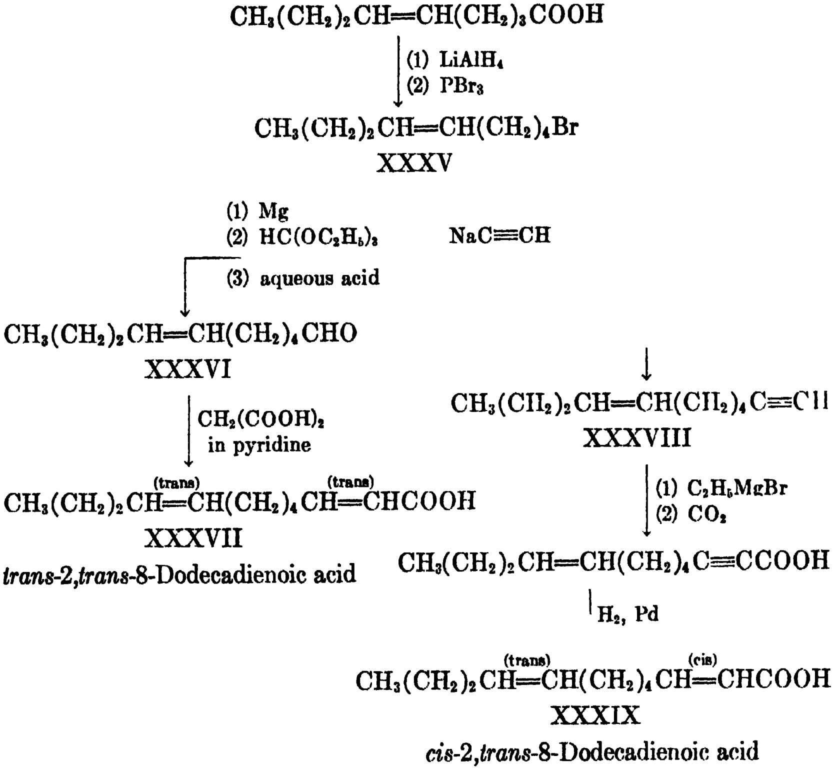
The acids with $\Delta^{8,9}$ trans were obtained (100) from *trans*-5-nonenyl bromide (XXXV). To get this material, the three-carbon chain of propylmagnesium bromide was extended by five carbon atoms by a standard procedure (Section II,F), involving coupling with 2,3-dichlorotetrahydropyran followed by treatment with powdered sodium. The *trans*-4-octen-1-ol (XXXIV) produced in this way in a stereospecific manner was converted by Grignardation and carbonation to *trans*-5-nonenoic acid, which after reduction with lithium aluminum hydride followed by treatment with phosphorus bromide gave the necessary bromide (XXXV). The trans,trans final product was reached by Grignardation, reaction with ethyl orthoformate, and hydrolysis to give the intermediate aldehyde (XXXVI), which in the Doebner reaction then gave *trans*-2,*trans*-8-dodecadienoic acid (XXXVII). The fourth stereoisomer was obtained by extending the carbon chain of the bromide XXXV with sodium acetylide, carbonating the Grignard derivative of the monosubstituted acetylene XXXVIII, and half-hydrogenating the resulting acetylenic α,β-unsaturated acid to *cis*-2, *trans*-8-dodecadienoic acid (XXXIX).


BrCH₂CH₂CH₂CH₂Br
(1) NaC≡CH
(2) NaNH₂
(3) CH₃CH₂CH₂Br
CH₃CH₂CH₂C≡C(CH₂)₄C≡CH
C₂H₅MgBr
CH₃CH₂CH₂C≡C(CH₂)₄C≡CMgBr
XXVIII
CO₂
(1) HC(OC₂H₅)₃
(2) H₂, Pd
CH₃CH₂CH₂C≡C(CH₂)₄C≡CCOOH
XXIX
H₂, Pd
(cis)
(cis)
CH₃CH₂CH₂CH=CH(CH₂)₄CH=CHCH(OC₂H₅)₂
XXXI
(cis)
(cis)
CH₃CH₂CH₂CH=CH(CH₂)₄CH=CHCOOH
XXX
H⁺, H₂O
(cis)
(trans)
CH₃CH₂CH₂CH=CH(CH₂)₄CH=CHCHO
XXXII
Ag₂O
(cis)
(trans)
CH₃CH₂CH₂CH=CH(CH₂)₄CH=CHCOOH
XXXIII
trans-2,cis-8-Dodecadienoic acid

A new synthesis of capsaicin (XL), isolated from red pepper, has been reported (107). The synthesis of the corresponding acid proceeds from *trans*-1-bromo-6-methyl-4-heptene, prepared by reactions analogous to those used for



XXXIV



$$CH_3(CH_2)_2CH{=}CH(CH_2)_3COOH \xrightarrow[(2)\ PBr_3]{(1)\ LiAlH_4} CH_3(CH_2)_2CH{=}CH(CH_2)_4Br$$

XXXV

$$CH_3(CH_2)_2CH{=}CH(CH_2)_4Br \xrightarrow[(3)\ \text{aqueous acid}]{(1)\ Mg;\ (2)\ HC(OC_2H_5)_3} CH_3(CH_2)_2CH{=}CH(CH_2)_4CHO$$

XXXVI

$$CH_3(CH_2)_2CH{=}CH(CH_2)_4CHO \xrightarrow[\text{in pyridine}]{CH_2(COOH)_2} CH_3(CH_2)_2\overset{(trans)}{CH{=}}CH(CH_2)_4\overset{(trans)}{CH{=}}CHCOOH$$

XXXVII

trans-2,*trans*-8-Dodecadienoic acid

$$CH_3(CH_2)_2CH{=}CH(CH_2)_4Br \xrightarrow{NaC{\equiv}CH} CH_3(CH_2)_2CH{=}CH(CH_2)_4C{\equiv}CH$$

XXXVIII

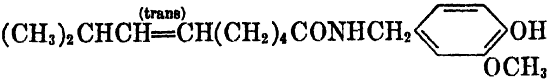
$$CH_3(CH_2)_2CH{=}CH(CH_2)_4C{\equiv}CH \xrightarrow[(2)\ CO_2]{(1)\ C_2H_5MgBr} CH_3(CH_2)_2CH{=}CH(CH_2)_4C{\equiv}CCOOH$$

$$CH_3(CH_2)_2CH{=}CH(CH_2)_4C{\equiv}CCOOH \xrightarrow{H_2,\ Pd} CH_3(CH_2)_2\overset{(trans)}{CH{=}}CH(CH_2)_4\overset{(cis)}{CH{=}}CHCOOH$$

XXXIX

cis-2,*trans*-8-Dodecadienoic acid

trans-5-nonenyl bromide (XXXV), by malonate chain extension.



$$(CH_3)_2CH\overset{(trans)}{CH{=}}CH(CH_2)_4CONHCH_2C_6H_3(OH)(OCH_3)$$

XL

Capsaicin

Affinin, another insecticidal principle, has been prepared (175) by elaborating the six-carbon acid, sorbic acid, in a standard sequence to *trans*-4,*trans*-6-octa-

$$CH_3\overset{(trans)}{CH{=}}CH\overset{(trans)}{CH{=}}CHCOOH \xrightarrow[(3)\ \text{malonate, etc.}]{(1)\ LiAlH_4;\ (2)\ PBr_3}$$

Sorbic acid

$$CH_3CH{=}CHCH{=}CHCH_2CH_2COOH \xrightarrow[(2)\ CrO_3]{(1)\ LiAlH_4}$$

XLI

$$CH_3CH{=}CHCH{=}CHCH_2CH_2CHO \xrightarrow[\text{in pyridine}]{CH_2(COOH)_2}$$

XLII

$$CH_3\overset{(trans)}{CH{=}}CH\overset{(trans)}{CH{=}}CHCH_2CH_2\overset{(trans)}{CH{=}}CHCOOH$$

XLIII

dienoic acid ((XLI), forming the corresponding aldehyde (XLII) by lithium aluminum hydride reduction to the alcohol followed by reoxidation by chromic oxide, and further extending the chain by application of the Doebner process. The isobutyl amide of the all-*trans*-2,6,8-decatrienoic acid (XLIII) so obtained was identical with affinin.

Synthesis of the isobutyl amides of *trans*-2,*trans*-4,*cis*-8-dodecatrienoic acid and of all-*trans*-2,4,8-dodecatrienoic acid by stereospecific methods similar to those described above has demonstrated that these amides are not the same as "sanshoöl I", an insecticide from *Zanthoxylum piperitum* D.C. (114).

D. ACETYLENIC ACIDS

1. *Stearolic and tariric acids*

Both simple (298) and complex acetylenic acids have been synthesized. For example, stearolic acid (9-octadecynoic acid), long known as the dehydrobromination product of oleic acid dibromide, has been prepared by crossed Kolbe syntheses from both 5-decynedioic acid (XLV: $n = 3$) and 6-dodecynedioic acid (XLV: $n = 4$). The former acid was prepared (31) by coupling the sodium derivative of 5-chloro-1-pentyne (XLIV: $n = 3$) with 1-bromo-3-chloropropane, and inserting terminal carboxyl groups by way of a nitrile process. 6-Dodecynedioic acid (XLV: $n = 4$) was prepared from 6-chloro-1-hexyne and 1-bromo-4-chlorobutane by analogous reactions (29). Crossed Kolbe coupling of methyl hydrogen 5-decynedioate (XLVI) with hexanoic acid gave methyl 5-tetradecynoate; the same process with methyl hydrogen adipate and 5-tetradecynoic acid (XLVII) added four carbon atoms and furnished methyl stearolate (XLVIII) (31). Crossed Kolbe combination of methyl hydrogen 6-dodecynoate (XLIX)

$$\underset{\text{XLIV}}{Cl(CH_2)_nC\equiv CH} \quad \begin{matrix}(1)\ NaNH_2\\ (2)\ Br(CH_2)_nCl\end{matrix},$$

$$Cl(CH_2)_nC\equiv C(CH_2)_nCl \xrightarrow[(3)\ \text{saponification}]{\begin{matrix}(1)\ NaI\\ (2)\ KCN\end{matrix}}$$

$$\underset{\text{XLV}}{HOOC(CH_2)_nC\equiv C(CH_2)_nCOOH}$$

$$\underset{\text{XLVI}}{HOOC(CH_2)_3C\equiv C(CH_2)_3COOCH_3} \quad \begin{matrix}CH_3(CH_2)_4COOH\\ \text{anodic oxidation}\end{matrix}.$$

$$CH_3(CH_2)_4(CH_2)_3C\equiv C(CH_2)_3COOCH_3 \xrightarrow{\text{hydrolysis}}$$

$$\underset{\text{XLVII}}{CH_3(CH_2)_7C\equiv C(CH_2)_3COOH} \xrightarrow[\text{anodic oxidation}]{HOOC(CH_2)_4COOCH_3}$$

$$\underset{\substack{\text{XLVIII}\\ \text{Methyl stearolate}}}{CH_3(CH_2)_7C\equiv C(CH_2)_3(CH_2)_4COOCH_3}$$

first with valeric acid and then with methyl hydrogen glutarate again furnished methyl stearolate (31). Crossed Kolbe combination of the same methyl hydrogen dodecynoate (XLIX) with octanoic acid gave the methyl ester (L) of tariric acid (from *Picramnia Sow*) directly (29). Tariric acid was also synthesized in another investigation (201) by a sequence essentially that of Ahmad and Strong (Section II,K).

$$HOOC(CH_2)_4C\equiv C(CH_2)_4COOCH_3$$

XLIX

$$\xrightarrow[\text{anodic oxidation}]{CH_3(CH_2)_3COOH} CH_3(CH_2)_7C\equiv C(CH_2)_4COOCH_3 \longrightarrow CH_3(CH_2)_7C\equiv C(CH_2)_4COOH$$

$$\xrightarrow[\text{(anodic oxidation)}]{HOOC(CH_2)_3COOCH_3} CH_3(CH_2)_7C\equiv C(CH_2)_7COOCH_3$$

XLVIII

Methyl stearolate

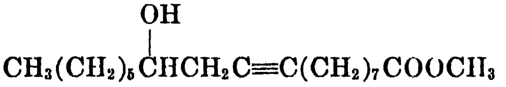
$$\xrightarrow[\text{anodic oxidation}]{CH_3(CH_2)_6COOH} CH_3(CH_2)_{10}C\equiv C(CH_2)_4COOCH_3$$

L

Methyl tarirate

2. *Ximenynic acid* (*santalbic acid*)

Both santalbic acid from sandal oil and ximenynic acid from several species of *Ximenia* and *Santalaceae* have been shown to have the structure of *trans*-11-octadecen-9-ynoic acid (LI) (*cf.* 149). Since ricinstearolic acid, which has been synthesized (Section III,H,1), has been converted with thionyl chloride to the corresponding chloro compound and then with alcoholic potassium hydroxide to ximenynic acid (113, 147), total synthesis of the latter may be claimed. Ximenynic acid or an isomer has also been obtained from methyl stearolate by brominating with *N*-bromosuccinimide on the 10- or the 8-position and heating to remove hydrogen bromide (216).



$$CH_3(CH_2)_5\overset{OH}{\overset{|}{C}}HCH_2C\equiv C(CH_2)_7COOCH_3 \xrightarrow[(2)\ KOH]{(1)\ SOCl_2} CH_3(CH_2)_5CH\overset{(trans)}{=}CHC\equiv C(CH_2)_7COOH$$

Methyl ricinstearolate

LI

Ximenynic acid

3. *Erythrogenic acid* (*isanic acid*)

Synthesis of erythrogenic acid (isanic acid), from the seed fat of *Onguekoa gore*, has been realized (39). The synthesis, in showing that the correct structure of erythrogenic acid is 17-octadecen-9,11-diynoic acid (LVII), disposed finally of an alternate possibility: namely, 17-octadecen-9,15-diynoic acid. 9-Decynoic acid (LIV), one of the moieties needed in the final stage of the synthesis, was prepared from 10-undecynoic ester (LII) by Barbier–Wieland degradation. Selective oxidative cleavage of intermediate ene-yne LIII (obtained as the dehydration product from the phenyl Grignard adduct) at the ethylenic unsaturation is noteworthy. The second moiety, 1-octen-7-yne (LVI), was formed by alkylating sodium acetylide with 4-chloro-1-iodo-butane (LV), half-hydrogenating the product, 6-chloro-1-hexyne, to 6-chloro-1-hexene, and combining the latter with sodium acetylide. Mixed Glaser coupling with 1-octen-7-yne (LVI) and 9-decynoic acid (LIV) gave the desired erythrogenic acid (LVII) as the cross product.

$$HC{\equiv}C(CH_2)_8COOC_2H_5 \xrightarrow[\text{(2) heat to 220°C.}]{\text{(1) } C_6H_5MgBr}$$

LII

$$HC{\equiv}C(CH_2)_7CH{=}C(C_6H_5)_2 \xrightarrow{CrO_3} HC{\equiv}C(CH_2)_7COOH$$

LIII LIV

9-Decynoic acid

$$I(CH_2)_4Cl \xrightarrow{NaC{\equiv}CH} HC{\equiv}CH(CH_2)_4Cl \xrightarrow[H_2]{Pd\text{-}CaCO_3}$$

LV

$$CH_2{=}CH(CH_2)_4Cl \xrightarrow[\text{(2) } NaC{\equiv}CH]{\text{(1) } NaI} CH_2{=}CH(CH_2)_4C{\equiv}CH$$

LVI

$$CH_2{=}CH(CH_2)_4C{\equiv}CH + HC{\equiv}C(CH_2)_7COOH \rightarrow$$

LVI LIV

1-Octen-7-yne 9-Decynoic acid

$$CH_2{=}CH(CH_2)_4C{\equiv}CC{\equiv}C(CH_2)_7COOH$$

LVII

Erythrogenic acid

4. Acids from Compositae

The accompanying formulas (LVIII to LXI) show some of the polyacetylenic compounds from various species of *Compositae*. The *trans*-2,*cis*-8 stereoisomer, as well as matricaria ester itself (LVIII), which is *cis*-2,*cis*-8, has been isolated (262). Interestingly enough, the *trans*-2,*trans*-8 isomer of matricaria ester can be extracted from a wood-rotting fungus (62). These and other naturally occurring polyacetylenic compounds have been authoritatively reviewed recently (41).

Synthetic work in this field has drawn heavily on and has benefitted greatly from recent developments in acetylene chemistry (*cf. inter alia* 232). Synthesis of a number of these compounds as well as of other more or less closely related polyacetylenes (13, 43, 60, 61, 95, 96, 159, 257) has been realized. To illustrate

$CH_3CH{=}CHC{\equiv}CC{\equiv}CCH{=}CHCOOCH_3$

LVIII

Matricaria ester

$CH_3CH{=}CHC{\equiv}CC{\equiv}CCH_2CH_2COOCH_3$

LIX

α,β-Dihydromatricaria ester

$CH_3CH{=}CHC{\equiv}CC{\equiv}CC{\equiv}CCOOCH_3$

LX

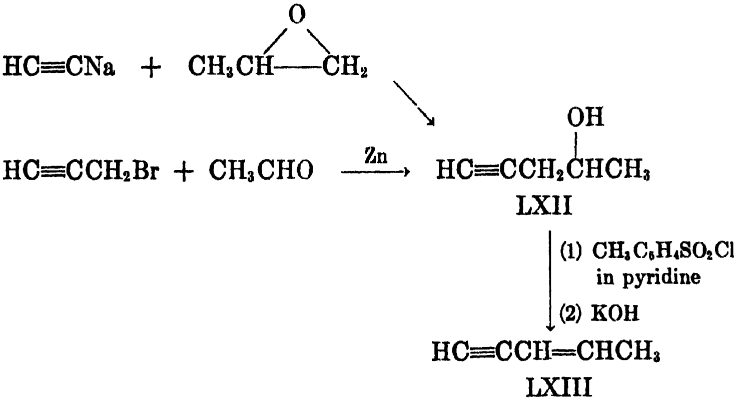
α,β-Dehydromatricaria ester

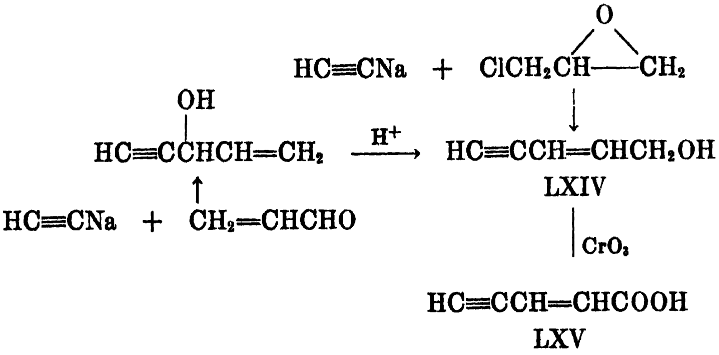
$CH_3CH_2CH_2C{\equiv}CC{\equiv}CCH{=}CHCOOCH_3$

LXI

Lachnophyllum ester

some of the reactions involved, the synthesis of two forms of matricaria ester is given below (60). 3-Penten-1-yne (LXIII), one of the intermediates needed for the final stage of the synthesis, was prepared by the two-stage dehydration of 4-pentyn-2-ol (LXII). This alcohol was prepared from acetylene and propylene oxide or from the zinc condensation of propargyl bromide and acetaldehyde. The second penultimate moiety, *trans*-2-penten-4-ynoic acid (LXV) was





prepared by controlled chromic oxide oxidation of the corresponding alcohol (LXIV). This was obtained from sodium acetylide and epichlorohydrin or, by acid-catalyzed rearrangement, from the condensation product of sodium acetylide and acrolein (95, 261). Glaser coupling of the methyl ester of *trans*-2-penten-4-ynoic acid and 3-penten-1-yne, which was a mixture of cis and trans forms, gave

$$CH_3CH{=}CHC{\equiv}CH \; + \; HC{\equiv}CCH{=}CHCOOCH_3 \; \rightarrow$$

$$CH_3CH{=}CHC{\equiv}CC{\equiv}CCH{=}CHCOOCH_3$$

LXVI

Matricaria ester

as the cross product a separable mixture of *trans*-2,*trans*-8- and *trans*-2,*cis*-8-matricaria ester (LXVI).

5. Isomycomycin

The structure of the antibiotic mycomycin (LXVII) has been elucidated (91). Although no synthesis of mycomycin has appeared, an elegant synthesis of isomycomycin (LXVIII), an isomerization product from mycomycin (90), has been completed (45) as follows: Lithium acetylide was added to pentadienal (LXIX) to give a secondary alcohol (LXX). Phosphorus tribromide converted alcohol LXX to primary bromide LXXI, which with cyanide in weakly acidic solution

$$HC{\equiv}CC{\equiv}CCH{=}C{=}CHCH{=}CHCH{=}CHCH_2COOH \xrightarrow{OH^-}$$

LXVII

Mycomycin

$$CH_3(C{\equiv}C)_3(CH{=}CH)_2CH_2COOH$$

LXVIII

Isomycomycin

$$CH_2{=}CHCH{=}CHCHO \quad LiC{\equiv}CH$$

LXIX

$$HC{\equiv}CCHOHCH{=}CHCH{=}CH_2 \xrightarrow{PBr_3}$$

LXX

$$HC{\equiv}CCH{=}CHCH{=}CHCH_2Br \xrightarrow{NaCN}$$

LXXI

$$HC{\equiv}CCH{=}CHCH{=}CHCH_2CN \quad \overset{CH_3C{\equiv}CC{\equiv}CH}{[O]}$$

LXXII

$$CH_3C{\equiv}CC{\equiv}CC{\equiv}CCH{=}CHCH{=}CHCH_2CN \xrightarrow[\text{(2) saponification}]{\text{(1) } CH_3OH\ (HCl)}$$

$$CH_3(C{\equiv}C)_3(CH{=}CH)_2CH_2COOH$$

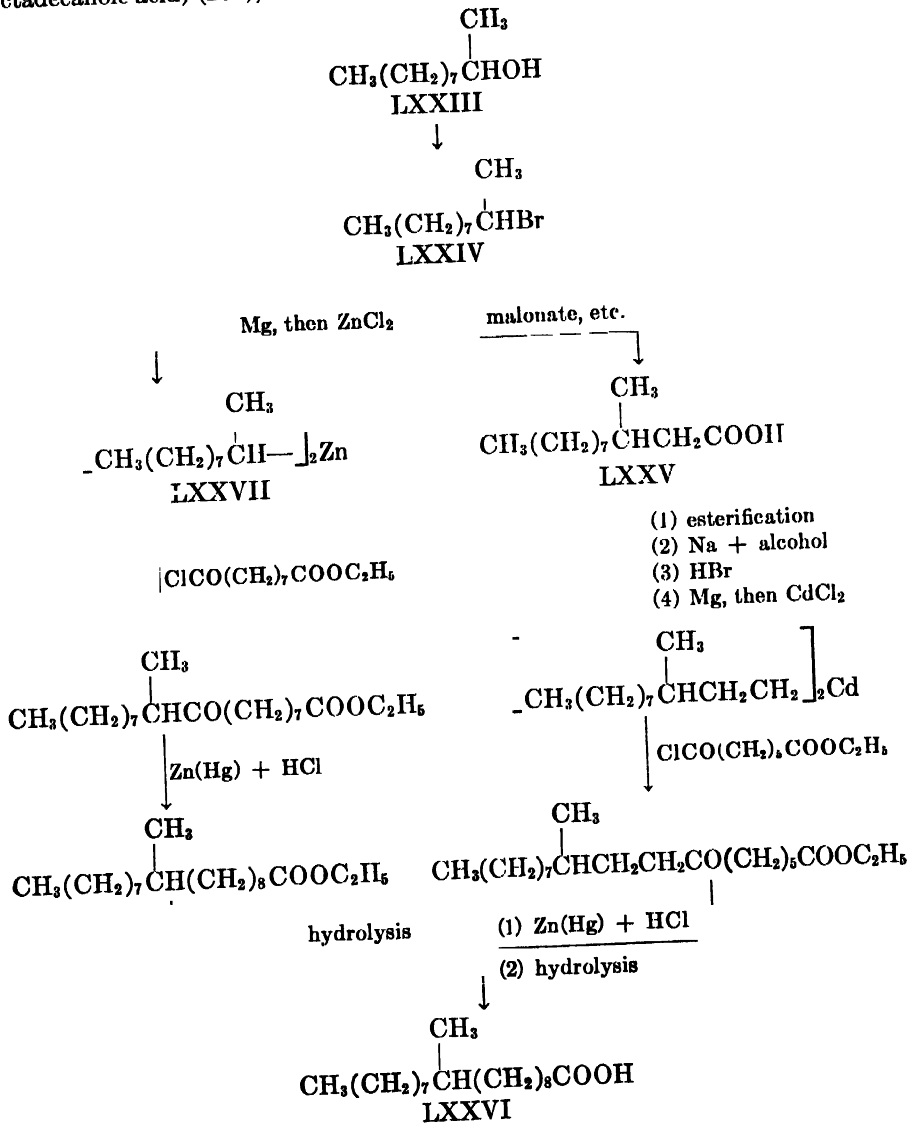
LXVIII

Isomycomycin

gave nitrile LXXII. Mixed Glaser coupling with 1,3-pentadiyne led to the nitrile of isomycomycin, and finally hydrolysis in two stages gave isomycomycin (LXVIII) itself. Other acids with a double bond conjugated to three triple bonds were synthesized by related reactions (45). Related model compounds—for example, methyl 3,5-tridecadienoate—have also been prepared (92).

E. TUBERCULOSTEARIC ACID (23)

Several different syntheses of tuberculostearic acid (LXXVI) (10-methyloctadecanoic acid) (266), one of the fatty acids isolated from the tubercle bacillus



$CH_3(CH_2)_7CH(CH_3)OH$

LXXIII

$CH_3(CH_2)_7CH(CH_3)Br$

LXXIV

Mg, then $ZnCl_2$

$[CH_3(CH_2)_7CH(CH_3)—]_2Zn$

LXXVII

$ClCO(CH_2)_7COOC_2H_5$

$CH_3(CH_2)_7CH(CH_3)CO(CH_2)_7COOC_2H_5$

Zn(Hg) + HCl

$CH_3(CH_2)_7CH(CH_3)(CH_2)_8COOC_2H_5$

hydrolysis

malonate, etc.

$CH_3(CH_2)_7CH(CH_3)CH_2COOH$

LXXV

(1) esterification
(2) Na + alcohol
(3) HBr
(4) Mg, then $CdCl_2$

$[CH_3(CH_2)_7CH(CH_3)CH_2CH_2]_2Cd$

$ClCO(CH_2)_5COOC_2H_5$

$CH_3(CH_2)_7CH(CH_3)CH_2CH_2CO(CH_2)_5COOC_2H_5$

(1) Zn(Hg) + HCl
(2) hydrolysis

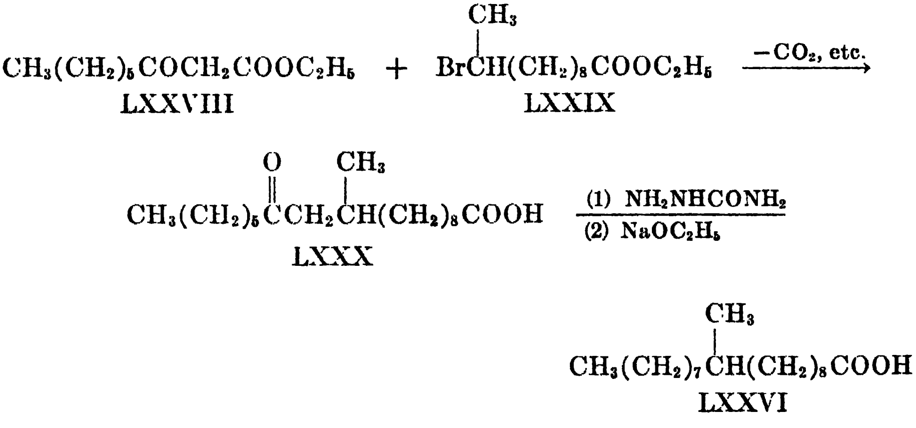
$CH_3(CH_2)_7CH(CH_3)(CH_2)_8COOH$

LXXVI

Tuberculostearic acid

(12, 84), have been reported. In one of the early syntheses (229; also *cf.* 266) 2-decanol (LXXIII) was the starting point. Extension of the chain by bromination and combination with sodiomalonate gave 3-methylundecanoic acid (LXXV). Ethyl 3-methylundecanoate was reduced (Bouveault–Blanc) to the alcohol, and the corresponding bromide converted in the usual way to the organocadmium derivative. Coupling with the acid chloride of ethyl hydrogen heptanedioate followed by Clemmensen reduction and hydrolysis gave tuberculostearic acid (LXXVI). Resolution of the starting alcohol (LXXIII) and again of the intermediate 3-methylundecanoic acid led to the optically active forms. An alternate conversion of the same 2-bromodecane (LXXIV) to tuberculostearic acid proceeded by coupling organozinc derivative LXXVII with the acid chloride of ethyl hydrogen nonanedioate (247). Clemmensen reduction of the resulting keto ester followed by hydrolysis of the ester gave tuberculostearic acid.

Bromo ester LXXIX, the hydrogen bromide addition product from 10-undecenoic acid, has the same features, including the methyl branch, as the first eleven carbon atoms of tuberculostearic acid. The terminal eight-carbon chain was attached by alkylating the β-keto ester LXXVIII with the bromo ester. 12-Oxotuberculostearic acid (LXXX), formed after hydrolysis and decarboxylation, was converted to tuberculostearic acid (LXXVI) by Wolff–Kishner reduction (15).



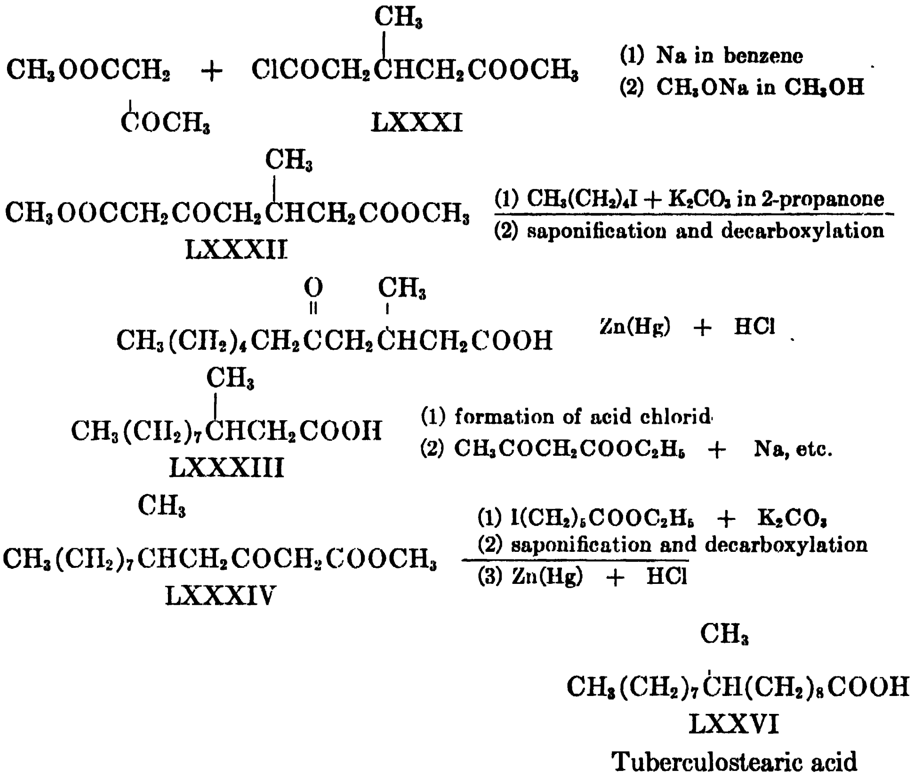
$$\underset{\text{LXXVIII}}{CH_3(CH_2)_5COCH_2COOC_2H_5} + \underset{\text{LXXIX}}{Br\overset{\displaystyle CH_3}{\overset{|}{C}}H(CH_2)_8COOC_2H_5} \xrightarrow{-CO_2,\ etc.}$$

$$\underset{\text{LXXX}}{CH_3(CH_2)_5\overset{\displaystyle O}{\overset{\|}{C}}CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}H(CH_2)_8COOH} \xrightarrow[(2)\ NaOC_2H_5]{(1)\ NH_2NHCONH_2}$$

$$\underset{\text{LXXVI}}{CH_3(CH_2)_7\overset{\displaystyle CH_3}{\overset{|}{C}}H(CH_2)_8COOH}$$

Tuberculostearic acid

3-Methylglutaric acid was the starting point in two other syntheses of tuberculostearic acid. In one report (269) the acid chloride (LXXXI) of methyl hydrogen glutarate was combined with acetoacetic ester in a standard acylation-deacetylation procedure to yield β-keto ester LXXXII. Alkylation of this β-keto ester with pentyl iodide, followed by saponification and decarboxylation, afforded 5-oxo-3-methylundecanoic acid, which by Clemmensen reduction gave 3-methylundecanoic acid (LXXXIII). This acid was converted to tuberculostearic acid by a series involving acylation, alkylation, and Clemmensen reduction (*cf.* LXXXIII, LXXXIV, and LXXVI). D-, L-, and racemic tuberculostearic acids were obtained in this work by starting, respectively, with the two optically active forms and with the racemic form of methyl hydrogen 3-methylglutarate.



$$\underset{\displaystyle COCH_3}{CH_3OOCCH_2} + \underset{\text{LXXXI}}{ClCOCH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2COOCH_3} \xrightarrow[\text{(2) }CH_3ONa\text{ in }CH_3OH]{\text{(1) Na in benzene}}$$

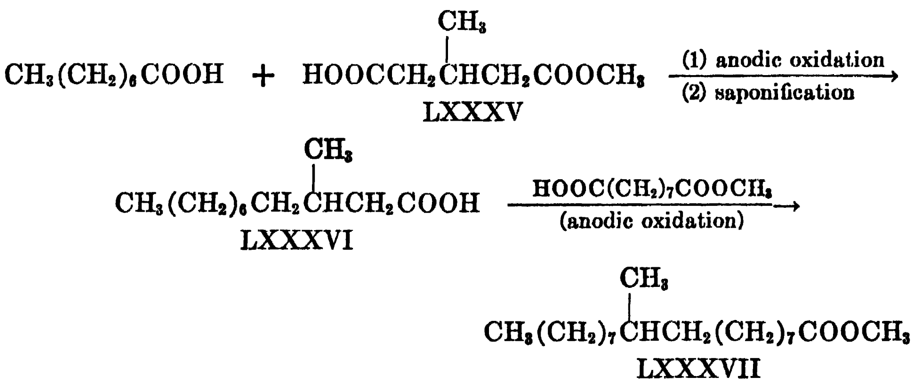
$$\underset{\text{LXXXII}}{CH_3OOCCH_2COCH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2COOCH_3} \xrightarrow[\text{(2) saponification and decarboxylation}]{\text{(1) }CH_3(CH_2)_4I + K_2CO_3\text{ in 2-propanone}}$$

$$CH_3(CH_2)_4CH_2\overset{\displaystyle O}{\overset{\|}{C}}CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2COOH \xrightarrow{Zn(Hg) + HCl}$$

$$\underset{\text{LXXXIII}}{CH_3(CH_2)_7\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2COOH} \xrightarrow[\text{(2) }CH_3COCH_2COOC_2H_5 + \text{Na, etc.}]{\text{(1) formation of acid chlorid}}$$

$$\underset{\text{LXXXIV}}{CH_3(CH_2)_7\overset{\displaystyle CH_3}{C}HCH_2COCH_2COOCH_3} \xrightarrow[\substack{\text{(2) saponification and decarboxylation}\\ \text{(3) }Zn(Hg) + HCl}]{\text{(1) }I(CH_2)_5COOC_2H_5 + K_2CO_3} \underset{\substack{\text{LXXVI}\\ \text{Tuberculostearic acid}}}{CH_3(CH_2)_7\overset{\displaystyle CH_3}{\overset{|}{C}}H(CH_2)_8COOH}$$

3-Methylglutaric acid could be elaborated to tuberculostearic acid in fewer steps by application of mixed Kolbe electrolyses (196). In the first stage octanoic

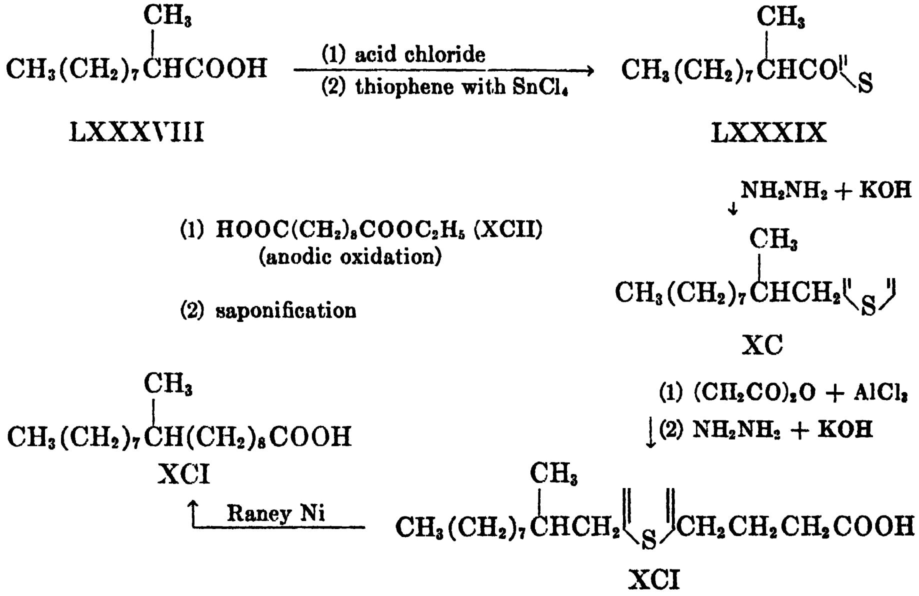


$$CH_3(CH_2)_6COOH + \underset{\text{LXXXV}}{HOOCCH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2COOCH_3} \xrightarrow[\text{(2) saponification}]{\text{(1) anodic oxidation}}$$

$$\underset{\text{LXXXVI}}{CH_3(CH_2)_6CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2COOH} \xrightarrow[\text{(anodic oxidation)}]{HOOC(CH_2)_7COOCH_3} \underset{\text{LXXXVII}}{CH_3(CH_2)_7\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2(CH_2)_7COOCH_3}$$

acid and methyl hydrogen 3-methylglutarate (LXXXV) were combined to form the cross product, 3-methylundecanoic methyl ester. The second stage combined 3-methylundecanoic acid (LXXXVI) with methyl hydrogen nonanedioate to generate methyl tuberculostearate (LXXXVII). Here, too, the use of optically active methyl hydrogen 3-methylglutarate led to optically active tuberculostearic acid (196).

Comparison of the three paths by which seven carbon atoms were added to 3-methylundecanoic acid (LXXV, LXXXIII, and LXXXVI) in its conversion to tuberculostearic acid is interesting. With azelaic acid readily available, the simplest procedure is clearly the mixed Kolbe reaction. The advantages of the Kolbe method receive further emphasis in the comparison of two pathways by which 2-methyldecanoic acid (LXXXVIII) has been converted to tuberculostearic acid. In one report (278), Friedel–Crafts combination of 2-methyl-

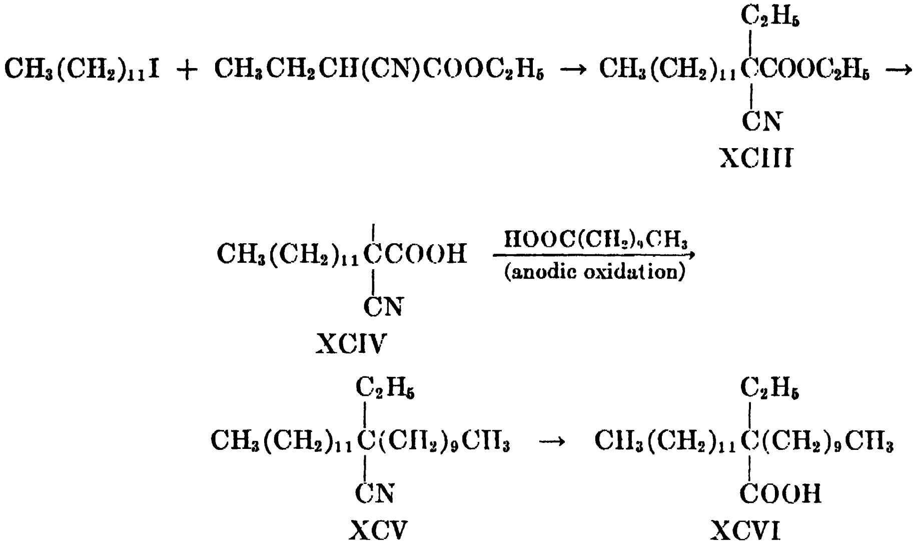


decanoyl chloride with thiophene gave the 2-acylthiophene LXXXIX, which by Wolff–Kishner reduction gave the 2-alkylthiophene XC. Friedel–Crafts reaction with succinic anhydride again followed by Wolff–Kishner reduction led to the disubstituted thiophene XCI. Treatment with excess Raney nickel removed sulfur and gave rise to tuberculostearic acid. This six-stage conversion is less convenient than mixed Kolbe coupling of 2-methyldecanoic acid with ethyl hydrogen sebacate (XCII) (20), which in a single stage led directly to methyl tuberculostearate.

F. "PHTHIOIC" ACID (23)

Phthioic acid is the name originally assigned to one of the fatty acids, $C_{26}H_{52}O_2$, from the tubercle bacillus (12, 267). Each of the several structures proposed was accepted seriously enough and survived long enough to stimulate considerable synthetic work. We find now, accordingly, that a large body of excellent synthetic work, especially on branched-chain acids, owes its existence to *incorrect* structures for phthioic acid.

An early suggestion (248, 267) that phthioic acid was a polymethylated fatty acid was challenged on the basis of physical evidence seemingly supporting a bulky molecule, such as a trialkylacetic acid, rather than an extended molecule (270). Among the acids considered was ethyldecyldodecylacetic acid (XCVI), a synthesis of which is given below (18; also *cf.* 16, 17). Alkylation of ethylcyanoacetic ester with dodecyl iodide gave a disubstituted cyanoacetic ester (XCIII). The corresponding acid (XCIV), serving as an unusual partner in mixed anodic oxidation with undecanoic acid, gave a trisubstituted acetonitrile (XCV) as the cross product. Hydrolysis in two stages led to the desired ethyldecyldodecylacetic acid (XCVI). Other kinds of syntheses for trisubstituted acetic acids also were developed (e.g., compare 64 and 265). None of the synthetic acids proved to be the same as phthioic acid.



$$CH_3(CH_2)_{11}I + CH_3CH_2CH(CN)COOC_2H_5 \rightarrow CH_3(CH_2)_{11}\overset{\overset{C_2H_5}{|}}{\underset{\underset{CN}{|}}{C}}COOC_2H_5 \rightarrow$$

XCIII

$$CH_3(CH_2)_{11}\overset{|}{\underset{\underset{CN}{|}}{C}}COOH \xrightarrow[\text{(anodic oxidation)}]{HOOC(CH_2)_9CH_3}$$

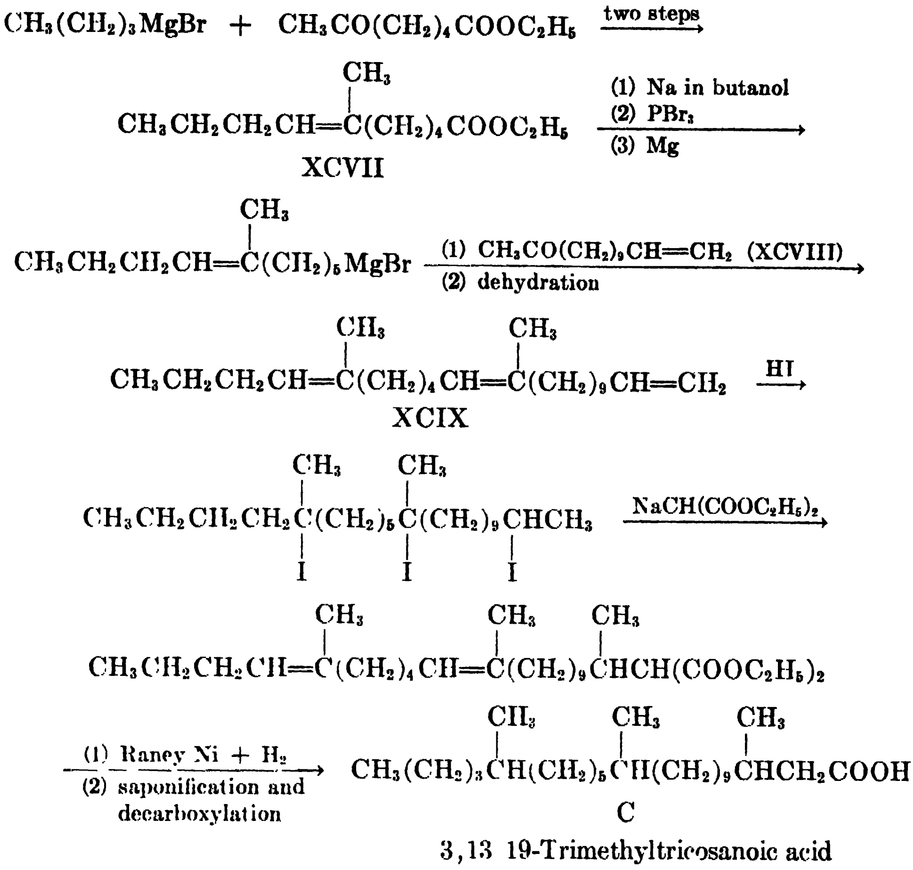
XCIV

$$CH_3(CH_2)_{11}\overset{\overset{C_2H_5}{|}}{\underset{\underset{CN}{|}}{C}}(CH_2)_9CH_3 \rightarrow CH_3(CH_2)_{11}\overset{\overset{C_2H_5}{|}}{\underset{\underset{COOH}{|}}{C}}(CH_2)_9CH_3$$

XCV XCVI

Ethyldecyldodecylacetic acid

Eventually, continued degradative work led to the conclusion that the proposed trialkylacetic acid structure was untenable, and that phthioic acid was actually 3,13,19-trimethyltricosanoic acid (225). Considerable effort was expended, subsequently, in exploring synthetic approaches. Two syntheses are described below, the first of which may be taken as illustrative of the earlier *modus operandi* of Robinson, Polgar, and their associates (118; also *cf.* 225, 226). Butylmagnesium bromide was added to 6-oxoheptanoic ester, and the resulting tertiary alcohol dehydrated to unsaturated ester XCVII. Bouveault–Blanc reduction furnished the expected alcohol, which was converted to the Grignard derivative via the bromide. Addition of the Grignard derivative to 12-tridecen-2-one (XCVIII) followed by dehydration gave the triene XCIX. The triiodide, formed by addition of hydriodic acid, reacted with sodiomalonate to bring about



$$CH_3(CH_2)_3MgBr + CH_3CO(CH_2)_4COOC_2H_5 \xrightarrow{\text{two steps}}$$

$$CH_3CH_2CH_2CH{=}\overset{\overset{\displaystyle CH_3}{|}}{C}(CH_2)_4COOC_2H_5 \xrightarrow[\text{(3) Mg}]{\text{(1) Na in butanol; (2) } PBr_3}$$

XCVII

$$CH_3CH_2CH_2CH{=}\overset{\overset{\displaystyle CH_3}{|}}{C}(CH_2)_5MgBr \xrightarrow[\text{(2) dehydration}]{\text{(1) } CH_3CO(CH_2)_9CH{=}CH_2 \text{ (XCVIII)}}$$

$$CH_3CH_2CH_2CH{=}\overset{\overset{\displaystyle CH_3}{|}}{C}(CH_2)_4CH{=}\overset{\overset{\displaystyle CH_3}{|}}{C}(CH_2)_9CH{=}CH_2 \xrightarrow{HI}$$

XCIX

$$CH_3CH_2CH_2CH_2\underset{\underset{\displaystyle I}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}(CH_2)_5\underset{\underset{\displaystyle I}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}(CH_2)_9\underset{\underset{\displaystyle I}{|}}{C}HCH_3 \xrightarrow{NaCH(COOC_2H_5)_2}$$

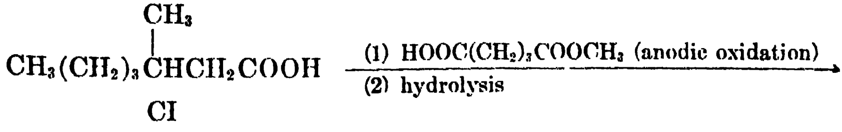
$$CH_3CH_2CH_2CH{=}\overset{\overset{\displaystyle CH_3}{|}}{C}(CH_2)_4CH{=}\overset{\overset{\displaystyle CH_3}{|}}{C}(CH_2)_9\overset{\overset{\displaystyle CH_3}{|}}{C}HCH(COOC_2H_5)_2$$

$$\xrightarrow[\text{(2) saponification and decarboxylation}]{\text{(1) Raney Ni} + H_2} CH_3(CH_2)_3\overset{\overset{\displaystyle CH_3}{|}}{C}H(CH_2)_5\overset{\overset{\displaystyle CH_3}{|}}{C}H(CH_2)_9\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2COOH$$

C

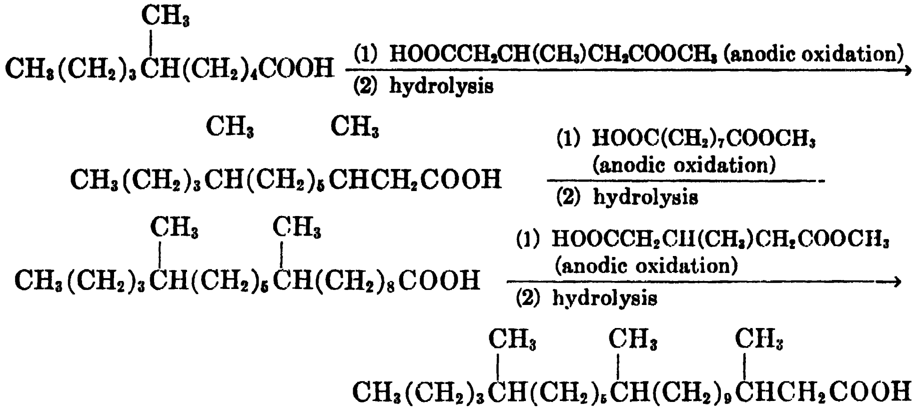
3,13 19-Trimethyltricosanoic acid

dehydrohalogenation at the two tertiary positions and alkylation of the malonate at the secondary position. The synthesis of 3,13,19-trimethyltricosanoic acid (C) was completed by hydrogenation of the ethylenic bonds, and by the usual saponification and decarboxylation treatment. Uncertainty as to the exact disposition of double bonds in the intermediates was of little consequence, since the final product was saturated. Lack of control of the stereochemistry at the branched positions, however, was more serious. Another method, proceeding by a cumulation of mixed Kolbe couplings, showed promise of overcoming this difficulty (199; also *cf.* 208, 211). By this scheme 3-methylheptanoic acid (CI) was coupled successively with methyl hydrogen glutarate, methyl hydrogen 3-methylglutarate, methyl hydrogen azelate, and again methyl hydrogen 3-methylglutarate to give finally 3,13,19-trimethyltricosanoic acid (C). Introduction of each center of asymmetry was both independent and controllable. This at-



$$CH_3(CH_2)_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2COOH \xrightarrow[\text{(2) hydrolysis}]{\text{(1) } HOOC(CH_2)_3COOCH_3 \text{ (anodic oxidation)}}$$

CI



$$\mathrm{CH_3(CH_2)_3\overset{CH_3}{\overset{|}{C}}H(CH_2)_4COOH} \xrightarrow[\text{(2) hydrolysis}]{\text{(1) }\mathrm{HOOCCH_2CH(CH_3)CH_2COOCH_3}\text{ (anodic oxidation)}}$$

$$\mathrm{CH_3(CH_2)_3\overset{CH_3}{C}H(CH_2)_5\overset{CH_3}{C}HCH_2COOH} \xrightarrow[\text{(2) hydrolysis}]{\text{(1) }\mathrm{HOOC(CH_2)_7COOCH_3}\text{ (anodic oxidation)}}$$

$$\mathrm{CH_3(CH_2)_3\overset{CH_3}{\overset{|}{C}}H(CH_2)_6\overset{CH_3}{\overset{|}{C}}H(CH_2)_8COOH} \xrightarrow[\text{(2) hydrolysis}]{\text{(1) }\mathrm{HOOCCH_2CH(CH_3)CH_2COOCH_3}\text{ (anodic oxidation)}}$$

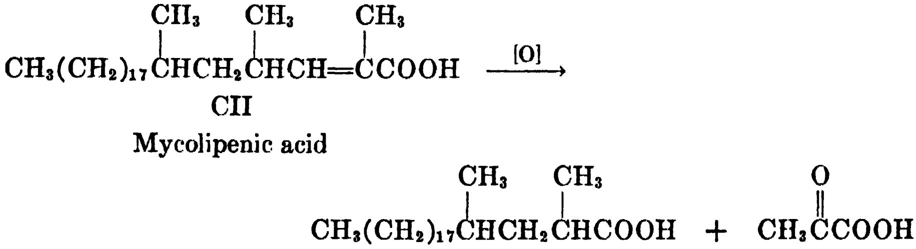
$$\mathrm{CH_3(CH_2)_3\overset{CH_3}{\overset{|}{C}}H(CH_2)_5\overset{CH_3}{\overset{|}{C}}H(CH_2)_9\overset{CH_3}{\overset{|}{C}}HCH_2COOH}$$

C

3,13,19-Trimethyltricosanoic acid

tractive series of reactions, which made attainment of stereochemically homogeneous material feasible, was however not pursued further, for evidence began to accumulate that phthioic acid was not a single substance but a mixture of several substances, possibly of many (82, 84, 93).

One group of investigators succeeded in isolating an *unsaturated* acid, which was named "mycolipenic acid" (93); another group isolated "C_{27}-phthienoic acid" (75), possibly (27) identical with mycolipenic acid. The assigned structure of mycolipenic acid (CII) rests on degradative evidence (94) and, in part, on synthesis. For example, oxidative cleavage at the double bond gave pyruvic acid as well as a new acid, 2,4-dimethyldocosanoic acid (CIII).



$$\mathrm{CH_3(CH_2)_{17}\overset{CH_3}{\overset{|}{C}}HCH_2\overset{CH_3}{\overset{|}{C}}HCH{=}\overset{CH_3}{\overset{|}{C}}COOH} \xrightarrow{[O]}$$

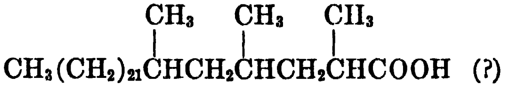
CII

Mycolipenic acid

$$\mathrm{CH_3(CH_2)_{17}\overset{CH_3}{\overset{|}{C}}HCH_2\overset{CH_3}{\overset{|}{C}}HCOOH} + \mathrm{CH_3\overset{O}{\overset{\|}{C}}COOH}$$

CIII

2, 4-Dimethyldocosanoic acid



$$\mathrm{CH_3(CH_2)_{21}\overset{CH_3}{\overset{|}{C}}HCH_2\overset{CH_3}{\overset{|}{C}}HCH_2\overset{CH_3}{\overset{|}{C}}HCOOH}\ (?)$$

CIV

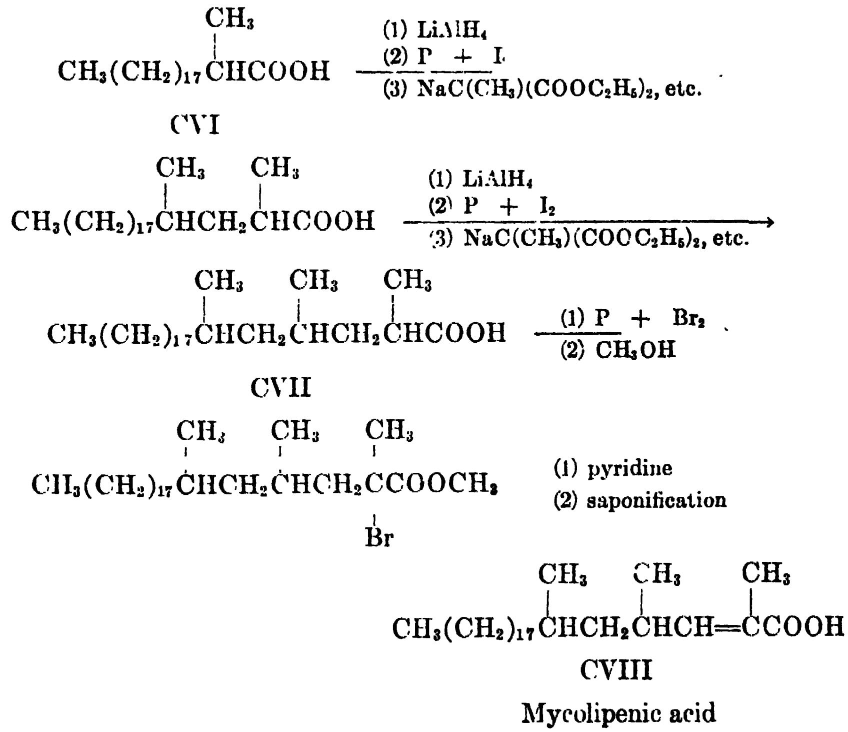
Mycoceranic acid

The structure of this last acid appears secure, inasmuch as a synthetic material proved to be identical with the degradation acid (130). "Mycoceranic acid"

(CIV) (224), another tubercle bacillus acid, was assigned the provisional structure of 2,4,6-trimethyloctacosanoic acid on the basis of degradation studies. From the several papers concerned with synthesis in this field (28, 69, 70, 73, 77, 177; also *cf.* Sections II,O,1, 2, II,Q, and II,A) only three, which are directly pertinent and which illustrate some of the reactions frequently used, have been selected for inclusion here.

A racemic mixture of acids stereoisomeric with, and presumably including, mycolipenic acid has been elaborated from octadecyl iodide (CV) (27). Alkylation of ethyl methylmalonate with this iodide, followed by the usual hydrolysis and decarboxylation, gave 2-methyleicosanoic acid (CVI). The series, reduction with lithium aluminum hydride, iodination with phosphorus and iodine, and malonate extension with methylmalonic ester, when applied twice afforded 2,4,6-trimethyltetracosanoic acid (CVII). Hell–Volhard–Zelinsky bromination on the α-position, followed by esterification, dehydrohalogenation with pyridine, and saponification, introduced the α,β-unsaturation and gave rise to the stereoisomers of 2,4,6-trimethyl-2-tetracosenoic acid (mycolipenic acid) (CVIII).

$$CH_3(CH_2)_{17}I \xrightarrow{NaC(CH_3)(COOC_2H_5)_2,\ etc.}$$



$$\underset{\text{CVI}}{CH_3(CH_2)_{17}\overset{\displaystyle CH_3}{\overset{|}{C}}HCOOH} \xrightarrow[(3)\ NaC(CH_3)(COOC_2H_5)_2,\ etc.]{(1)\ LiAlH_4\quad (2)\ P\ +\ I_2}$$

$$CH_3(CH_2)_{17}\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCOOH \xrightarrow[(3)\ NaC(CH_3)(COOC_2H_5)_2,\ etc.]{(1)\ LiAlH_4\quad (2)\ P\ +\ I_2}$$

$$\underset{\text{CVII}}{CH_3(CH_2)_{17}\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCOOH} \xrightarrow[(2)\ CH_3OH]{(1)\ P\ +\ Br_2}$$

$$CH_3(CH_2)_{17}\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2\underset{\displaystyle Br}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}COOCH_3 \xrightarrow[(2)\ saponification]{(1)\ pyridine}$$

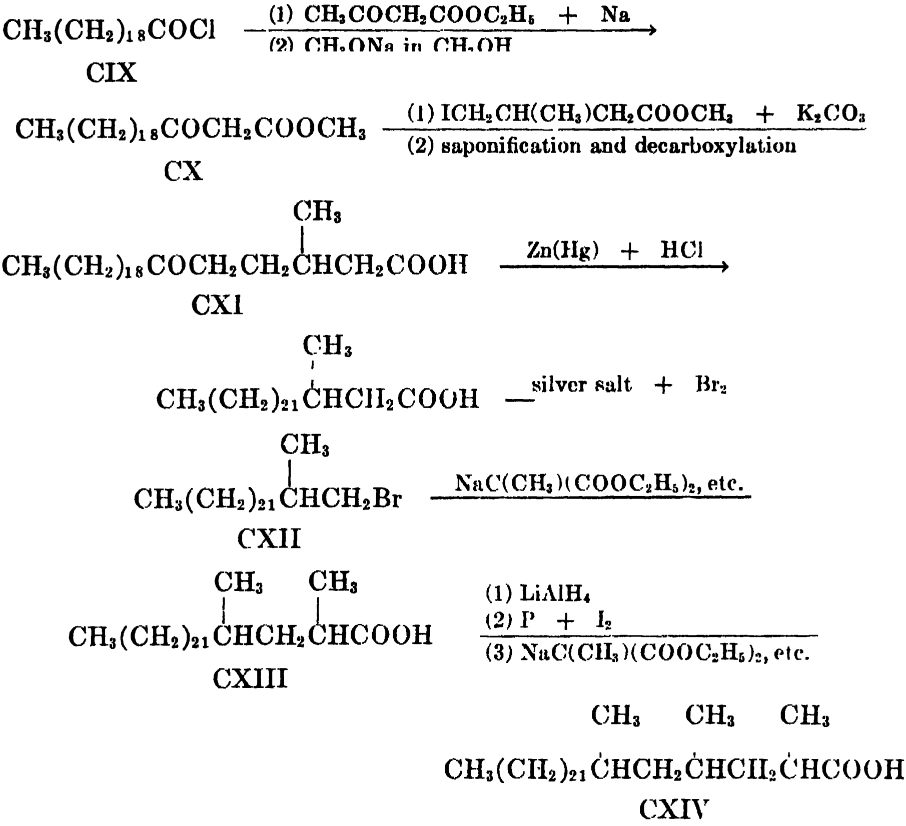
$$CH_3(CH_2)_{17}\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCH{=}\overset{\displaystyle CH_3}{\overset{|}{C}}COOH$$

CVIII

Mycolipenic acid

A mixture of the stereoisomers of 2,4,6-trimethyloctacosanoic acid (CXIV), possibly including mycoceranic acid, has been synthesized from eicosanoic acid

(203). The twenty-carbon acid chloride CIX was converted to the twenty-two carbon β-keto ester CX by combination with acetoacetic ester followed by deacetylation. Alkylation of the β-keto ester with optically active 4-iodo-3-methylbutyric ester (derived from optically active methyl hydrogen 3-methylglutarate) led to optically active 3-methyl-6-oxopentacosanoic acid (CXI). Clemmensen reduction removed the ketone oxygen and gave 3-methylpentacosanoic acid. Decarboxylation of the silver salt with bromine gave the alkyl bromide CXII, which in the malonate process with methylmalonate was converted to 2,4-dimethylhexacosanoic acid (CXIII). Reduction with lithium aluminum hydride, iodination with phosphorus and iodine, and finally alkylation of methylmalonate led to the desired acid (CXIV). The center of asymmetry at the 6-position was in a single stereochemical configuration; both forms of the centers at 2 and at 4 were present. The product mixture could be described therefore as 2,4,6-(D)-trimethyloctacosanoic acid.



$$CH_3(CH_2)_{18}COCl \xrightarrow[\text{(2) } CH_3ONa \text{ in } CH_3OH]{\text{(1) } CH_3COCH_2COOC_2H_5 \ + \ Na}$$

CIX

$$CH_3(CH_2)_{18}COCH_2COOCH_3 \xrightarrow[\text{(2) saponification and decarboxylation}]{\text{(1) } ICH_2CH(CH_3)CH_2COOCH_3 \ + \ K_2CO_3}$$

CX

$$CH_3(CH_2)_{18}COCH_2CH_2\overset{\overset{\Large CH_3}{|}}{C}HCH_2COOH \xrightarrow{Zn(Hg) \ + \ HCl}$$

CXI

$$CH_3(CH_2)_{21}\overset{\overset{\Large CH_3}{|}}{C}HCH_2COOH \xrightarrow{\text{silver salt} \ + \ Br_2}$$

$$CH_3(CH_2)_{21}\overset{\overset{\Large CH_3}{|}}{C}HCH_2Br \xrightarrow{NaC(CH_3)(COOC_2H_5)_2\text{, etc.}}$$

CXII

$$CH_3(CH_2)_{21}\overset{\overset{\Large CH_3}{|}}{C}HCH_2\overset{\overset{\Large CH_3}{|}}{C}HCOOH \xrightarrow[\text{(3) } NaC(CH_3)(COOC_2H_5)_2\text{, etc.}]{\text{(1) } LiAlH_4 \quad \text{(2) } P \ + \ I_2}$$

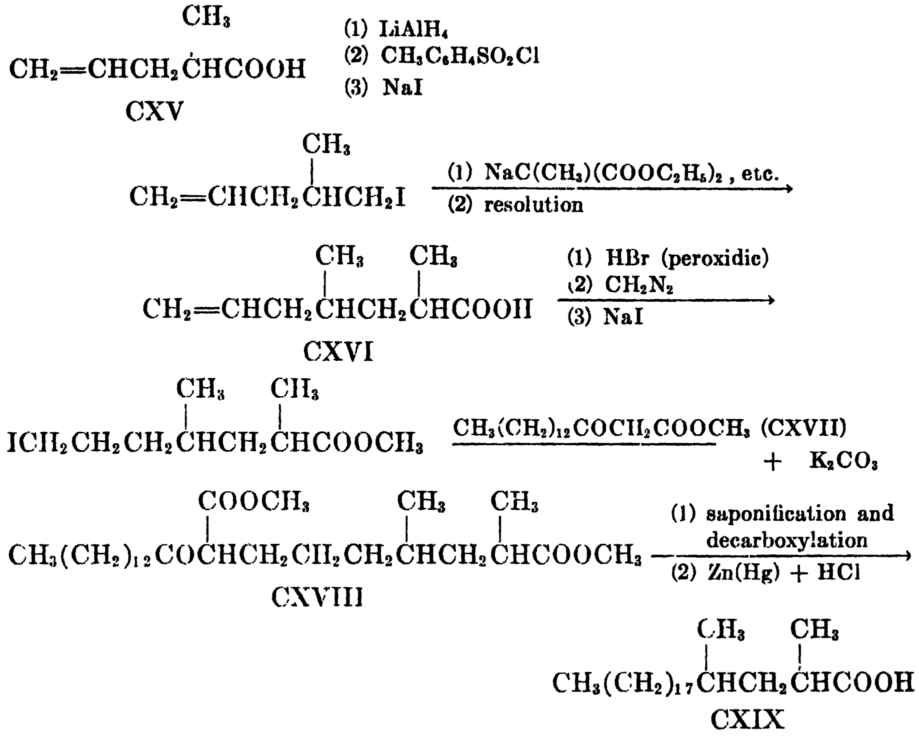
CXIII

$$CH_3(CH_2)_{21}\overset{\overset{\Large CH_3}{|}}{C}HCH_2\overset{\overset{\Large CH_3}{|}}{C}HCH_2\overset{\overset{\Large CH_3}{|}}{C}HCOOH$$

CXIV

2,4,6-Trimethyloctacosanoic acid

Optically active 2,4-dimethyldocosanoic acid (CIII), a key degradation product from mycolipenic acid, was synthesized as follows (130): Optically active 2-methyl-4-pentenoic acid (CXV) was converted to 2-methyl-4-pentenyl iodide by reduction with lithium aluminum hydride, tosylation of the alcohol,



$$\underset{\text{CXV}}{CH_2{=}CHCH_2\overset{CH_3}{\overset{|}{C}}HCOOH} \xrightarrow[(3)\ NaI]{(1)\ LiAlH_4\quad (2)\ CH_3C_6H_4SO_2Cl}$$

$$CH_2{=}CHCH_2\overset{CH_3}{\overset{|}{C}}HCH_2I \xrightarrow[(2)\ \text{resolution}]{(1)\ NaC(CH_3)(COOC_2H_5)_2,\ \text{etc.}}$$

$$\underset{\text{CXVI}}{CH_2{=}CHCH_2\overset{CH_3}{\overset{|}{C}}HCH_2\overset{CH_3}{\overset{|}{C}}HCOOH} \xrightarrow[(3)\ NaI]{(1)\ HBr\ (\text{peroxidic})\quad (2)\ CH_2N_2}$$

$$ICH_2CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_2\overset{CH_3}{\overset{|}{C}}HCOOCH_3 \xrightarrow[+\ K_2CO_3]{CH_3(CH_2)_{12}COCH_2COOCH_3\ (\text{CXVII})}$$

$$\underset{\text{CXVIII}}{CH_3(CH_2)_{12}CO\overset{COOCH_3}{\overset{|}{C}}HCH_2CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_2\overset{CH_3}{\overset{|}{C}}HCOOCH_3} \xrightarrow[(2)\ Zn(Hg)\ +\ HCl]{(1)\ \text{saponification and decarboxylation}}$$

$$\underset{\text{CXIX}}{CH_3(CH_2)_{17}\overset{CH_3}{\overset{|}{C}}HCH_2\overset{CH_3}{\overset{|}{C}}HCOOH}$$

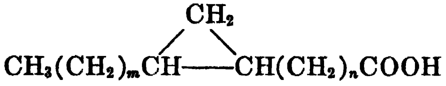
2,4-Dimethyldocosanoic acid

and replacement of the tosyloxy group with iodide. Alkylation of methylmalonate gave 2,4-dimethyl-6-heptenoic acid (CXVI), which on resolution gave the optically pure material. Peroxidic addition of hydrogen bromide formed the ω-bromide. The methyl ester, after conversion to the iodide, was used to alkylate the β-keto ester CXVII. Hydrolysis of the alkylation product (CXVIII), followed by decarboxylation and Clemmensen reduction, gave acid CXIX. Recrystallization with quinine led to dextrorotatory 2,4-dimethyldocosanoic acid, identical with the oxidation product (CIII) from mycolipenic acid. Since the formal synthesis of mycolipenic acid could be completed by its reconstitution from optically active 2,4-dimethyldocosanoic acid, which may now be obtained from degradation as a relay intermediate, and since reliable methods are available for converting RCOOH to $RCH{=}C(CH_3)COOH$, the prognosis for the successful total synthesis of mycolipenic acid is good.

G. CYCLOALKYL FATTY ACIDS

Syntheses of compounds related to lactobacillic acid (23) and to the antileprosy acids have been reported. Interest in the synthesis of vitamin A, as well as of carotenes in general, has continued unabated.

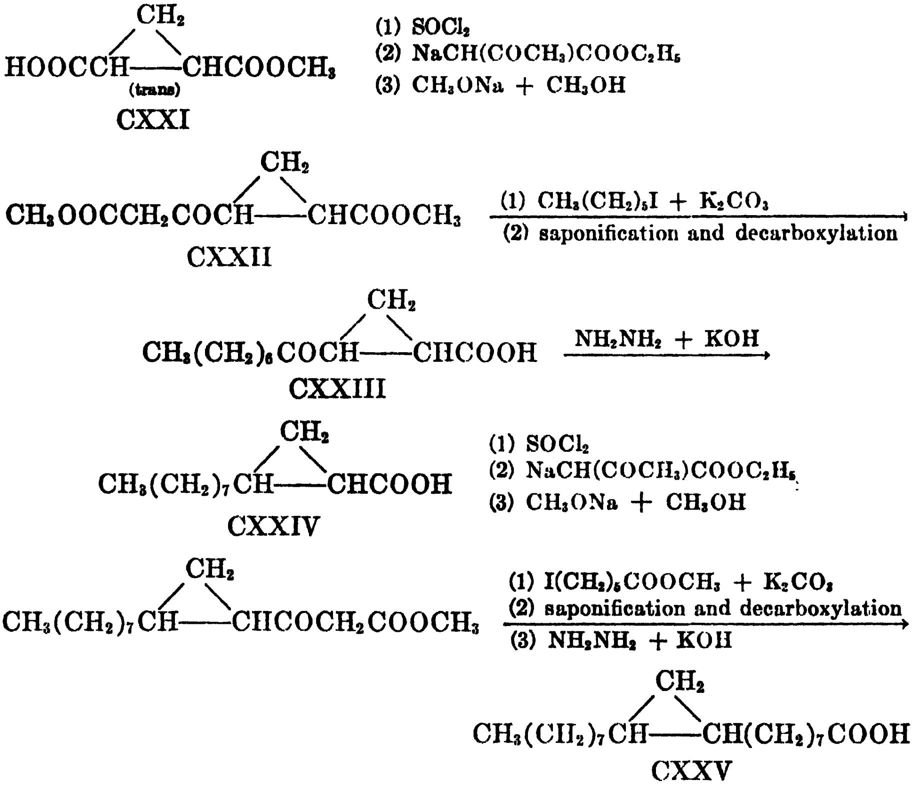
Lactobacillic acid, a C_{19} acid from *Lactobacillus arabinosus*, contains a cyclopropane ring and is thought to have the structure shown in formula CXX (161). One possibility, with $m = n = 7$, has been synthesized starting with *trans*-cyclopropane-1,2-dicarboxylic acid (161) and building outwards from both



CXX

Lactobacillic acid: $m + n = 14$

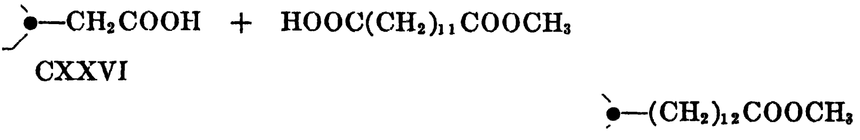
carboxyl groups. The acid chloride of methyl hydrogen *trans*-cyclopropane-1,2-dicarboxylate (CXXI) was used to acylate acetoacetic ester. Deacetylation by methanolysis furnished the β-keto ester CXXII, which on alkylation with hexyl iodide, saponification, and decarboxylation gave the keto acid CXXIII. Wolff-Kishner reduction led to *trans*-2,3-methyleneundecanoic acid (CXXIV). Very



trans-9,10-Methyleneoctadecanoic acid

much the same kind of process of first extending the carboxylic acid by two carbon atoms by forming a β-keto ester and then extending the chain further by alkylating the β-keto ester, etc., gave the desired *trans*-9,10-methyleneoctadecanoic acid (CXXV). This compound was not the same as lactobacillic acid, but did show points of similarity. Further, neither *trans*-11,12-methyleneoctadecanoic acid, prepared by an analogous synthesis, nor *cis*-9,10-methyleneoctadecanoic acid, prepared by hydrogenating sterculic acid, a cyclopropene acid, was identical with lactobacillic acid.

Chaulmoogric acid (207) and other cycloalkyl and cycloalkenyl fatty acids (183, 212, 296) have been prepared by mixed Kolbe couplings. For example,

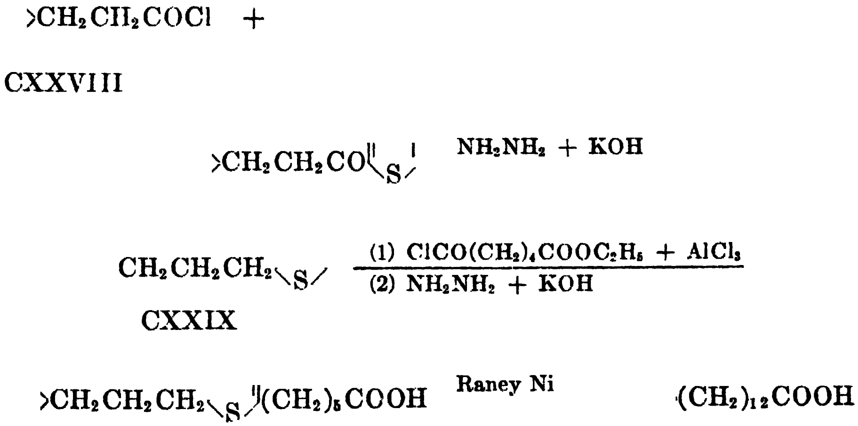


CXXVI

CXXVII
Chaulmoogric ester

dextrorotatory 2-cyclopenteneacetic acid (CXXVI) anodically oxidized with methyl hydrogen tridecanedioate gave dextrorotatory chaulmoogric ester (CXXVII), identical with the natural product (207). This synthesis showed that the configuration in natural chaulmoogric acid and that in cyclopentenylacetic acid (CXXVI) are the same. Accordingly, determination of the configuration in the latter established the configuration of chaulmoogric acid, as indicated in formula CXXVII.

Thiophene intermediates were involved in new syntheses of dihydrochaulmoogric acid and related compounds (65). Formulas CXXVIII to CXXXI show how 2-(cyclopentylpropyl)thiophene (CXXIX) was prepared from cyclopentylpropionyl chloride and thiophene by Friedel–Crafts acylation followed by



CXXVIII

CXXIX

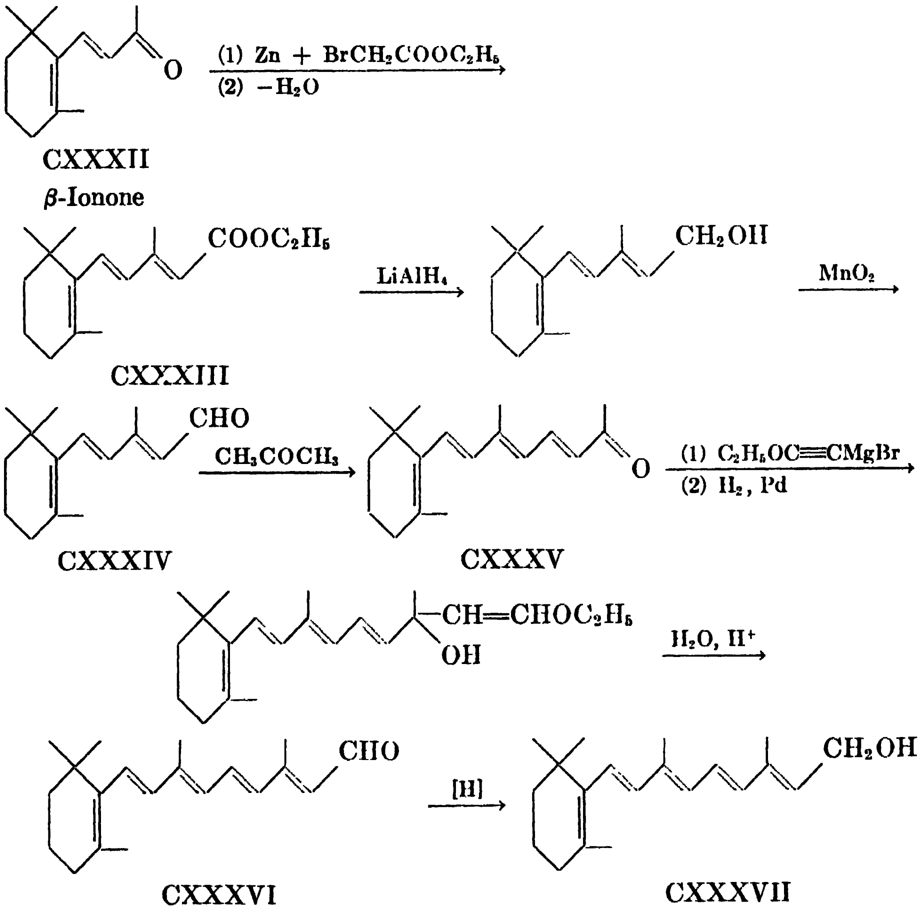
CXXX

CXXXI
Dihydrochaulmoogric acid

Wolff–Kishner reduction. Disubstituted thiophene CXXX was prepared by acetylating cyclopentylpropylthiophene with the acid chloride of ethyl hydrogen adipate and again removing the acyl oxygen with hydrazine and potassium hydroxide. Desulfurization with Raney nickel (Section II,H) furnished dihydrochaulmoogric acid (CXXXI).

For the present purpose, the various syntheses of vitamin A may be looked upon as extensions of a methyl-substituted chain by methods eventually providing a geometrically correct conjugated system terminating in an oxygen function. In this light, much if not all of the extensive synthetic work on vitamin A (and, in general, on carotenoids) is of immediate or potential interest in the synthesis of cyclic, branched, unsaturated, or saturated fatty acids. However, because reviews of vitamin A and of carotenoids are available (35, 54, 172, 181, 251), illustrations of only two syntheses will be given.

In one preparation of vitamin A, two carbon atoms were added to β-ionone (CXXXII) by Reformatsky addition of bromoacetic ester followed by loss of water. The resulting fifteen-carbon ester (CXXXIII) was converted to the corresponding fifteen-carbon aldehyde (CXXXIV) by reduction with lithium aluminum hydride followed by reoxidation with manganese dioxide. Aldehyde



CXXXII
β-Ionone

CXXXIII

CXXXIV

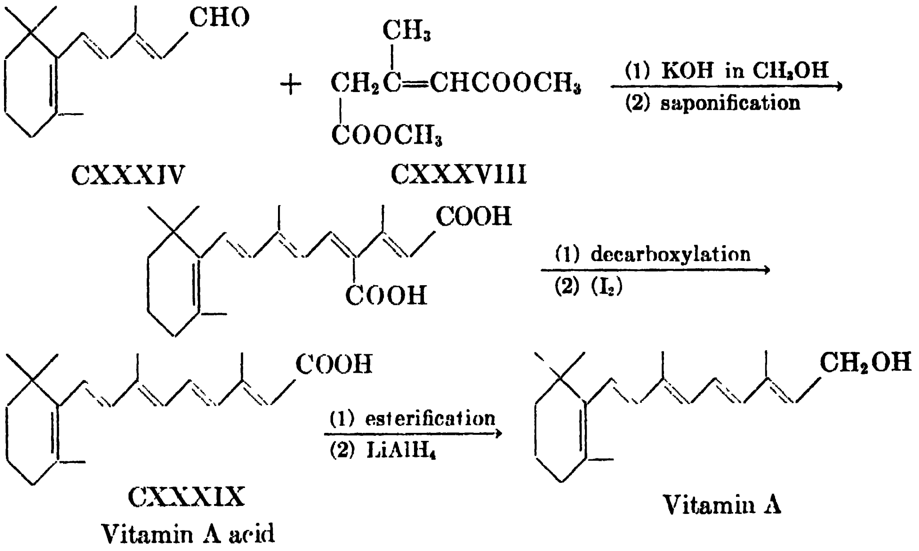
CXXXV

CXXXVI
Vitamin A aldehyde

CXXXVII
Vitamin A

CXXXIV, condensed with acetone, afforded an eighteen-carbon methyl ketone (CXXXV). Addition of ethoxyacetylenemagnesium bromide, half-hydrogenation of the product to the vinyl ether, and hydrolysis in aqueous acid gave vitamin A aldehyde (CXXXVI), which on reduction gave vitamin A (CXXXVII).

In another synthesis (242) the fifteen-carbon aldehyde CXXXIV was extended by one isoprene unit by alkali-catalyzed condensation with dimethyl 3-methylglutaconate (CXXXVIII) followed by decarboxylation. The single cis bond in the product was isomerized under iodine catalysis to the all-trans vitamin A acid (CXXXIX), which was then reduced with lithium aluminum hydride to vitamin A.



CXXXIV

CXXXVIII

CXXXIX
Vitamin A acid

Vitamin A

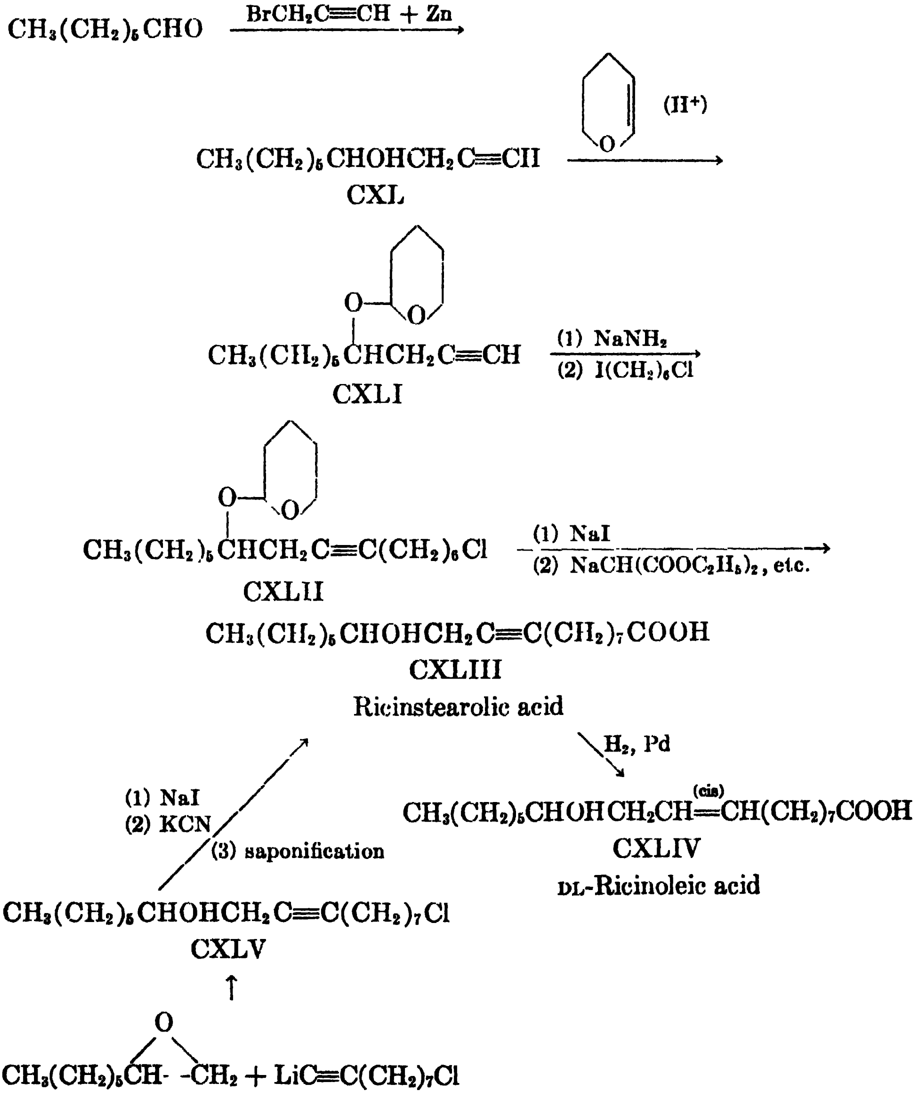
H. HYDROXY ACIDS

Activity in synthetic work on hydroxy acids has been considerable. Syntheses of, or relating to, ricinoleic acid, phloionolic acid, 9,10-dihydroxystearic acid, and mycolic acids have been reported. General methods for the preparation of β-hydroxy acids have been developed and exploited. All seventeen of the hydroxystearic acids have been made available. Synthetic pathways leading to unsaturated acids by way of intermediate hydroxy acids have been explored. Stereospecific conversion of vicinal glycols to ethylenic compounds (Section II,O,5) was found to be both general and useful.

The broad topic of oxygen-substituted fatty acids, including hydroxy acids, has been ably summarized by Swern (275).

1. *Ricinoleic acid*

Ricinoleic acid (12-hydroxy-*cis*-9-octadecenoic acid) (CXLIV) has been synthesized. According to one report (113), heptaldehyde and propargyl bromide were combined in a Reformatsky-like process to form 1-decyn-4-ol (CXL). The hydroxyl hydrogen was replaced with the tetrahydropyran group, and the resulting terminal acetylenic derivative (CXLI) combined with 1-chloro-6-iodohexane in the usual manner. The iodide corresponding to the sixteen-carbon chloride CXLII was converted to ricinstearolic acid (CXLIII) by the application of the malonate synthesis supplemented by mild acid treatment to expose the alcohol group. Half-hydrogenation of ricinstearolic acid gave racemic ricinoleic acid (CXLIV). Ricinstearolic acid (CXLIII) could also be obtained (133) by adding the lithium derivative of 9-chloro-1-nonyne to 1,2-epoxyoctane. The intermediate CXLV was converted to ricinstearolic acid by the nitrile synthesis.


$CH_3(CH_2)_6CHO$
$BrCH_2C{\equiv}CH + Zn$
$CH_3(CH_2)_6CHOHCH_2C{\equiv}CH$
(H+)
O
$CH_3(CH_2)_6CHCH_2C{\equiv}CH$
(1) $NaNH_2$
(2) $I(CH_2)_6Cl$
$CH_3(CH_2)_6CHCH_2C{\equiv}C(CH_2)_6Cl$
(1) NaI
(2) $NaCH(COOC_2H_5)_2$, etc.
$CH_3(CH_2)_5CHOHCH_2C{\equiv}C(CH_2)_7COOH$
H_2, Pd
(cis)
$CH_3(CH_2)_5CHOHCH_2CH{=}CH(CH_2)_7COOH$
(1) NaI
(2) KCN
(3) saponification
$CH_3(CH_2)_5CHOHCH_2C{\equiv}C(CH_2)_7Cl$
$CH_3(CH_2)_5CH\text{-}\text{-}CH_2 + LiC{\equiv}C(CH_2)_7Cl$

CXL

CXLI

CXLII

CXLIII
Ricinstearolic acid

CXLIV
DL-Ricinoleic acid

CXLV

Another synthesis was characterized by operations on the carboxyl side of the molecule instead of on the methyl side (184). Coupling of 8-chloro-1-octyne

(CXLVI) with bromoacetal gave the acetylenic acetal CXLVII. The cis ethylenic aldehyde CXLVIII was obtained by half-hydrogenation followed by acid-catalyzed hydrolysis of the acetal grouping. Addition of hexylmagnesium bromide to the aldehyde developed the β-hydroxy olefin system as in CXLIX, and extension of the chain by application of the malonate process led to ricinoleic acid (CL).

$$HC\equiv C(CH_2)_6Cl \xrightarrow[(2)\ BrCH_2CH(OCH_3)_2]{(1)\ LiNH_2}$$

CXLVI

$$(CH_3O)_2CHCH_2C\equiv C(CH_2)_6Cl \quad \begin{matrix}(1)\ H_2,\ Pd\\ (2)\ H_2O,\ H^+\end{matrix}$$

CXLVII

$$O{=}CHCH_2\overset{(cis)}{CH{=}}CH(CH_2)_6Cl \xrightarrow{CH_3(CH_2)_5MgBr}$$

CXLVIII

$$CH_3(CH_2)_5CHOHCH_2CH{=}CH(CH_2)_6Cl \quad \begin{matrix}(1)\ NaI\\ (2)\ NaCH(COOC_2H_5)_2,\ \text{etc.}\end{matrix}$$

CXLIX

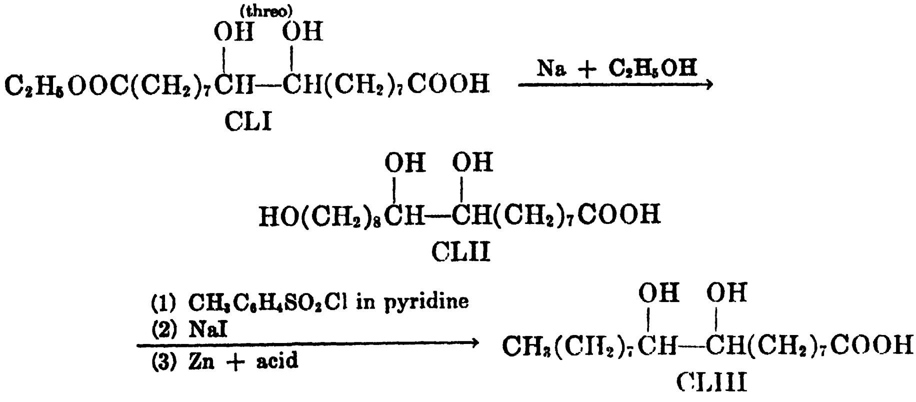
$$CH_3(CH_2)_5CHOHCH_2CH{=}CH(CH_2)_7COOH$$

CL

DL-Ricinoleic acid

2. 9,10-Dihydroxystearic acid

Phloionic acid (9,10-dihydroxyoctadecanedioic acid), from cork, was proved by synthesis (140) and by resolution (141) to have the threo configuration. The half-ester (CLI) of phloionic acid was converted to 9,10,18-trihydroxystearic acid (CLII), which by selective tosylation on the primary hydroxyl, replacement



$$C_2H_5OOC(CH_2)_7\overset{\overset{(threo)}{OH}}{\overset{|}{C}H}-\overset{OH}{\overset{|}{C}H}(CH_2)_7COOH \xrightarrow{Na\ +\ C_2H_5OH}$$

CLI

$$HO(CH_2)_8\overset{OH}{\overset{|}{C}H}-\overset{OH}{\overset{|}{C}H}(CH_2)_7COOH$$

CLII

$$\xrightarrow[(3)\ Zn\ +\ acid]{(1)\ CH_3C_6H_4SO_2Cl\ in\ pyridine\\ (2)\ NaI} CH_3(CH_2)_7\overset{OH}{\overset{|}{C}H}-\overset{OH}{\overset{|}{C}H}(CH_2)_7COOH$$

CLIII

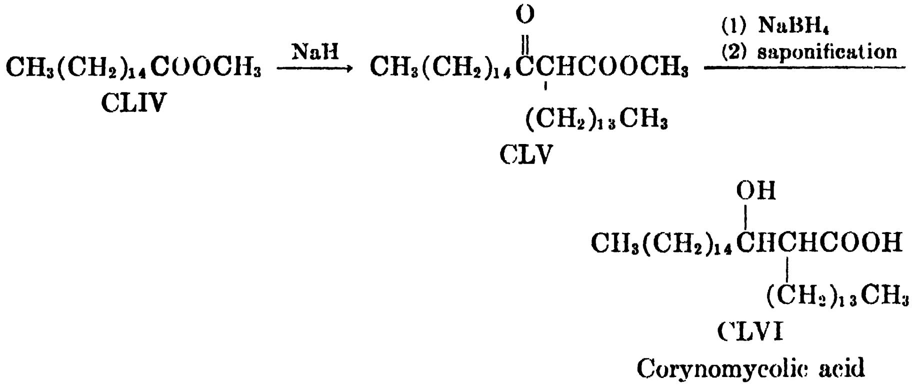
threo-9,10-Dihydroxystearic acid

of the tosyloxy group by iodide, and dehalogenation with zinc gave 9,10-dihydroxystearic acid (CLIII), m.p. 94–95°C. Since the configuration at the 9- and 10-positions was not disturbed, these conversions established the threo nature of "low-melting" 9,10-dihydroxystearic acid. Arguments have been presented

(141) that the structure of phloionolic acid, also isolated from cork, may not be that of 9,10,18-trihydroxystearic acid (CLII).

3. Corynomycolic and related acids (23)

Corynomycolic acid, $C_{32}H_{64}O_3$, has been isolated from the lipide from *Corynebacterium diphtheriae*. This fatty acid has structural features in common with various "mycolic acids" from *Mycobacteria*: namely, a long chain at the α-position and hydroxyl at the β-position. The synthesis of corynomycolic acid described below (191, 227) is illustrative of considerable work on the mycolic acids and related compounds. β-Keto ester CLV was obtained by Claisen condensation



$$CH_3(CH_2)_{14}COOCH_3 \xrightarrow{NaH} CH_3(CH_2)_{14}\overset{O}{\overset{\|}{C}}\underset{(CH_2)_{13}CH_3}{CH}COOCH_3 \xrightarrow[(2)\ \text{saponification}]{(1)\ NaBH_4} CH_3(CH_2)_{14}\overset{OH}{CH}\underset{(CH_2)_{13}CH_3}{CH}COOH$$

CLIV

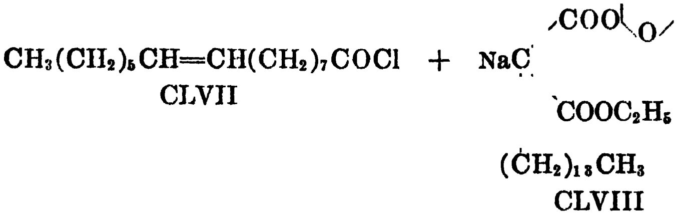
CLV

CLVI

Corynomycolic acid

(with sodium hydride) of methyl palmitate (CLIV). Reduction of the keto group with sodium borohydride or with hydrogen over a catalyst led to the β-hydroxy ester, which on saponification gave hydroxy acid CLVI. Separation of the two racemates was effected either at the hydroxy ester or hydroxy acid stage by recrystallization and chromatography. One of the racemates proved to be *dl*-corynomycolic acid (CLVI). Homologation of this material was possible by the Arndt–Eistert method (123) (see Section II,A).

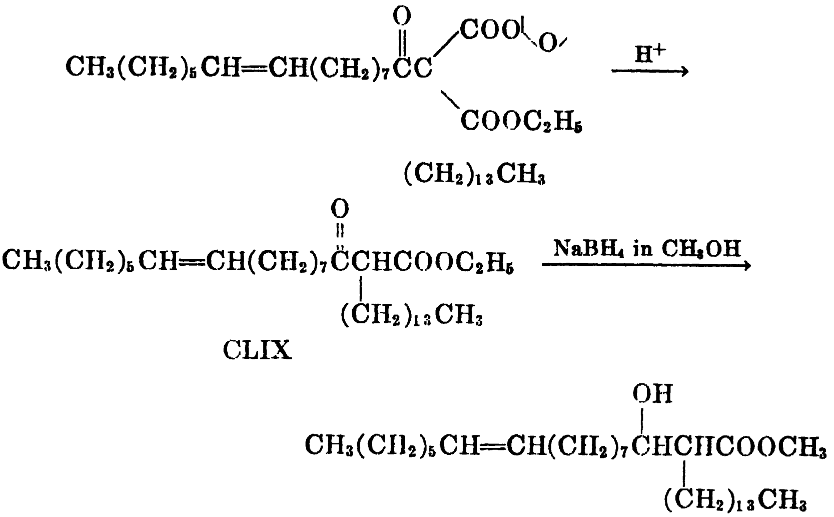
β-Keto esters derived formally from two different esters were formed by applying a scheme developed by Bowman and Fordham (see Section II,J,2). For example, keto ester CLIX was prepared by acylating malonic acid derivative CLVIII with acid chloride CLVII, and exposing the product to the action of mild aqueous acid. Sodium borohydride reduction gave hydroxy ester CLX, which showed an infrared absorption spectrum identical with that of methyl corynomycolenate (230; also *cf.* 123).



$$CH_3(CH_2)_5CH{=}CH(CH_2)_7COCl + Na\underset{(CH_2)_{13}CH_3}{C}(COO\text{-}C(CH_3)_3)(COOC_2H_5)$$

CLVII

CLVIII



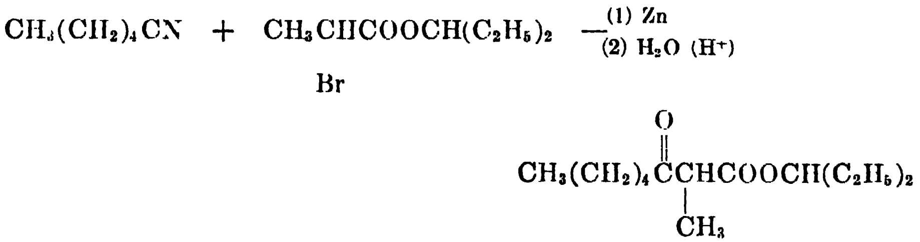
$$\mathrm{CH_3(CH_2)_5CH{=}CH(CH_2)_7\overset{\overset{O}{\|}}{C}\underset{\underset{(CH_2)_{13}CH_3}{|}}{C}HCOOC_2H_5} \xrightarrow{\mathrm{NaBH_4\ in\ CH_3OH}}$$

CLIX

$$\mathrm{CH_3(CH_2)_5CH{=}CH(CH_2)_7\overset{\overset{OH}{|}}{C}H\underset{\underset{(CH_2)_{13}CH_3}{|}}{C}HCOOCH_3}$$

CLX

A reaction of potential usefulness for the preparation of such compounds as CLIX carries out a zinc condensation of an α-bromo ester not with an aldehyde or ketone as in the familiar Reformatsky process, but with a nitrile (81). In this way, for example, capronitrile with α-bromopropionic ester gave the α-methyl β-keto ester CLXI. Bulky groups in the bromo ester, either in the alkyl attached to the carboxyl group or in the α-position, promoted the process instead of hindering it.

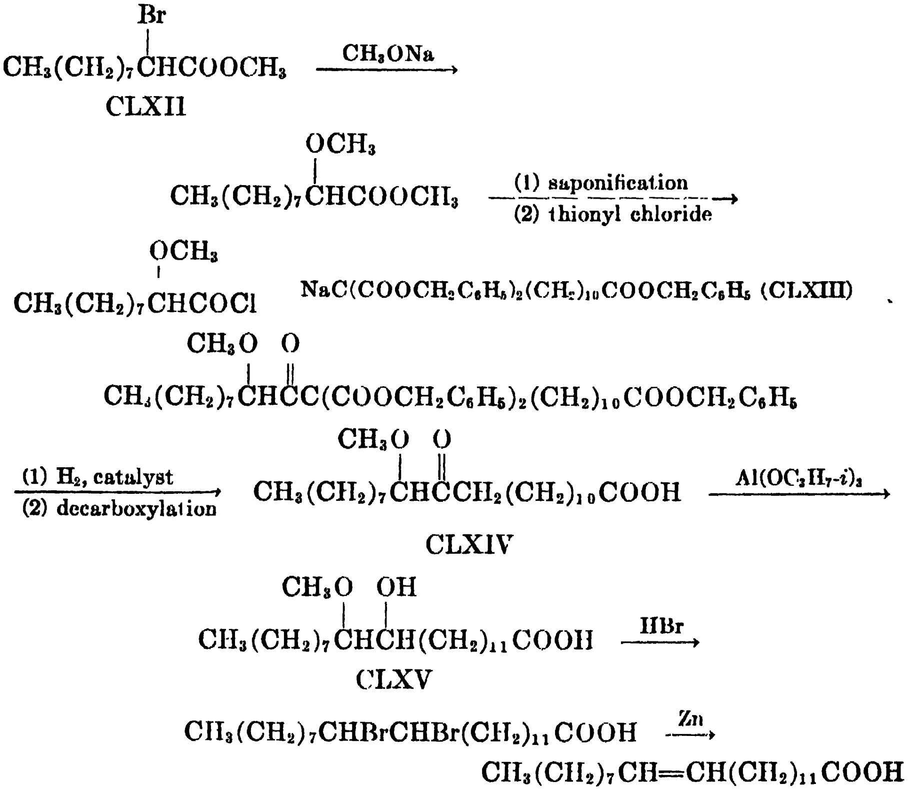


$$\mathrm{CH_3(CH_2)_4CN} + \mathrm{CH_3\underset{\underset{Br}{|}}{C}HCOOCH(C_2H_5)_2} \xrightarrow[\text{(2) H}_2\text{O (H}^+\text{)}]{\text{(1) Zn}} \mathrm{CH_3(CH_2)_4\overset{\overset{O}{\|}}{C}\underset{\underset{CH_3}{|}}{C}HCOOCH(C_2H_5)_2}$$

CLXI

4. Hydroxy acids prepared according to Ames and Bowman: utilization of such acids for the introduction of ethylenic unsaturation

Two methods have been developed for the synthesis of vicinal dihydroxy acids and monomethoxylated vicinal dihydroxy acids. Such compounds can be converted by standard processes to olefinic acids (Section II,O,5). The synthesis of brassidic and erucic acids (*trans-* and *cis*-13-docosenoic acids (CLXVI)) via a vicinal methoxy hydroxy intermediate will illustrate one of the methods (52). Methyl 2-bromodecanoate (CLXII), obtained by the bromination of decanoic acid, was converted to 2-methoxydecanoyl chloride, and then by way of the substituted malonic ester (CLXIII) to 14-methoxy-13-oxodocosanoic acid (CLXIV) according to the method described in Section II,J,2. Reduction of this ketone with aluminum isopropoxide gave a mixture of two stereoisomeric 13-hydroxy-14-methoxydocosanoic acids (CLXV). In this case (but not in all) the two forms could be separated by fractional crystallization. Hydrogen bromide converted the individual methoxy alcohols to the corresponding 13,14-dibromodocosanoic acids, which by debromination with zinc gave brassidic and erucic acids (CLXVI). In much the same way 2-methoxydecanoic acid was combined with the tribenzyl ester of heptane-1,1,7-tricarboxylic acid to give eventually oleic and elaidic acids (8; also *cf.* 9).



$$CH_3(CH_2)_7\overset{\overset{\displaystyle Br}{|}}{C}HCOOCH_3 \xrightarrow{CH_3ONa}$$

CLXII

$$CH_3(CH_2)_7\overset{\overset{\displaystyle OCH_3}{|}}{C}HCOOCH_3 \xrightarrow[\text{(2) thionyl chloride}]{\text{(1) saponification}}$$

$$CH_3(CH_2)_7\overset{\overset{\displaystyle OCH_3}{|}}{C}HCOCl \xrightarrow{NaC(COOCH_2C_6H_5)_2(CH_2)_{10}COOCH_2C_6H_5\ (CLXIII)}$$

$$CH_3(CH_2)_7\overset{\overset{\displaystyle CH_3O}{|}}{C}H\overset{\overset{\displaystyle O}{\|}}{C}C(COOCH_2C_6H_5)_2(CH_2)_{10}COOCH_2C_6H_5$$

$$\xrightarrow[\text{(2) decarboxylation}]{\text{(1) } H_2\text{, catalyst}} CH_3(CH_2)_7\overset{\overset{\displaystyle CH_3O}{|}}{C}H\overset{\overset{\displaystyle O}{\|}}{C}CH_2(CH_2)_{10}COOH \xrightarrow{Al(OC_3H_7\text{-}i)_3}$$

CLXIV

$$CH_3(CH_2)_7\overset{\overset{\displaystyle CH_3O}{|}}{C}H\overset{\overset{\displaystyle OH}{|}}{C}H(CH_2)_{11}COOH \xrightarrow{HBr}$$

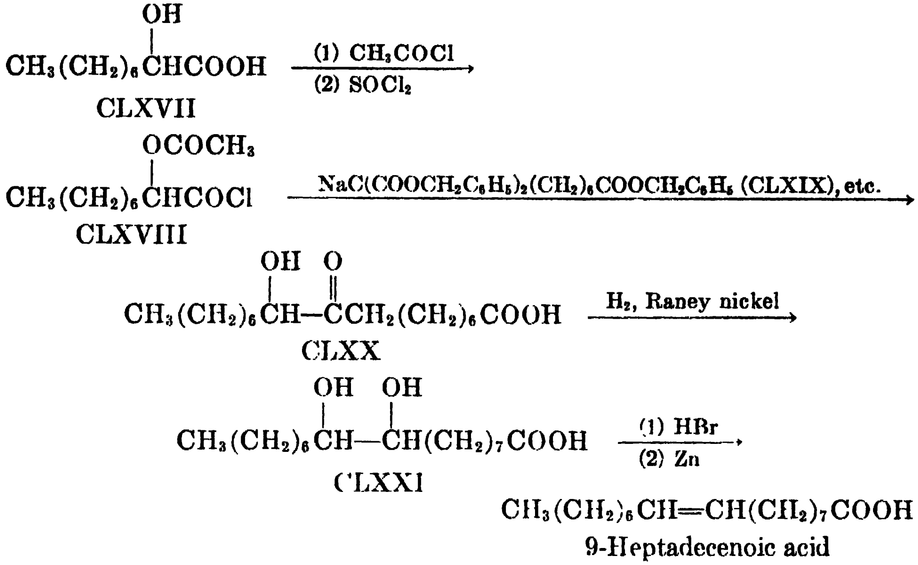
CLXV

$$CH_3(CH_2)_7CHBrCHBr(CH_2)_{11}COOH \xrightarrow{Zn} CH_3(CH_2)_7CH{=}CH(CH_2)_{11}COOH$$

CLXVI

Brassidic and erucic acids

The second method (8) makes use not of the methoxy acid but of the acetoxy acid, and, although closely related to the method just described, is somewhat more attractive because of more convenient stereochemical control. The synthesis of pure *cis*-9-heptadecenoic and *trans*-9-heptadecenoic acids proceeded by reaction of 2-hydroxynonanoic acid (CLXVII) (from the 2-bromo acid) first with acetyl chloride to give the 2-acetoxy acid and then with thionyl chloride to give the acid chloride (CLXVIII). Combination of the acid chloride with substituted malonic ester (CLXIX), followed by hydrogenolysis, loss of two molecules of carbon dioxide, and deacetylation gave 10-hydroxy-9-oxoheptadecanoic acid (CLXX). A mixture of two dihydroxy acids (CLXXI) was obtained on reduction either with hydrogen and Raney nickel or with aluminum isopropoxide. However, separation of the two solid forms by fractional crystallization was straightforward. Treatment of the pure threo and the pure erythro dihydroxy acids (CLXXI) with hydrobromic acid to form the homogeneous dibromides, and then with zinc to bring about debromination, produced pure *trans*-9-heptadecenoic and *cis*-9-heptadecenoic acids, respectively.



$$\mathrm{CH_3(CH_2)_6\overset{OH}{\overset{|}{C}}HCOOH} \xrightarrow[\text{(2) SOCl}_2]{\text{(1) CH}_3\text{COCl}}$$

CLXVII

$$\mathrm{CH_3(CH_2)_6\overset{OCOCH_3}{\overset{|}{C}}HCOCl} \xrightarrow{\mathrm{NaC(COOCH_2C_6H_5)_2(CH_2)_6COOCH_2C_6H_5}\text{ (CLXIX), etc.}}$$

CLXVIII

$$\mathrm{CH_3(CH_2)_6\overset{OH}{\overset{|}{C}}H{-}\overset{O}{\overset{\|}{C}}CH_2(CH_2)_6COOH} \xrightarrow{\text{H}_2\text{, Raney nickel}}$$

CLXX

$$\mathrm{CH_3(CH_2)_6\overset{OH}{\overset{|}{C}}H{-}\overset{OH}{\overset{|}{C}}H(CH_2)_7COOH} \xrightarrow[\text{(2) Zn}]{\text{(1) HBr}}$$

CLXXI

$$\mathrm{CH_3(CH_2)_6CH{=}CH(CH_2)_7COOH}$$

9-Heptadecenoic acid

5. *Miscellaneous hydroxy acids*

β-Hydroxy acids have been prepared by Reformatsky coupling of α-bromo esters and carbonyl compounds (*cf.* 59. 80, 83, 104, 150, 169, 176, 177, 209, 242). For example, a series of β-hydroxy α-methyl acids, β-hydroxy β-methyl acids, and β-hydroxy α,β-dimethyl acids was made available (59) by zinc condensation of aldehydes and α-bromopropionic ester, of methyl ketones and bromoacetic ester, and of methyl ketones and α-bromopropionic ester, respectively.

Skogh (258) has prepared β-hydroxy acids by hydrogenating the corresponding β-keto ester (i.e., CLXXII to CLXXIII). The keto esters were obtained by acylating acetoacetic ester with a straight-chain acid chloride and then deacetylating (see Section II,J,1). In the accompanying formulas R ranges from

$$\mathrm{RCOCl} \xrightarrow[\text{(2) NaOCH}_3\text{ + CH}_3\text{OH}]{\text{(1) NaCH(COCH}_3\text{)COOC}_2\text{H}_5} \mathrm{RCOCH_2COOCH_3}$$

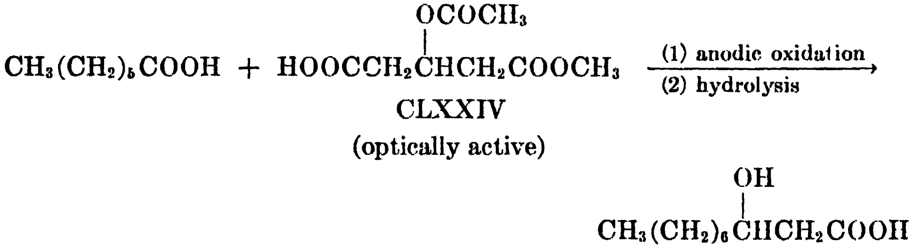
CLXXII

$$\xrightarrow[\text{(2) hydrolysis}]{\text{(1) Raney Ni + H}_2} \mathrm{RCHOHCH_2COOH}$$

CLXXIII

pentyl to heneicosyl, so that all linear β-hydroxy acids from C_8 to C_{24} were prepared. Further examples of the preparation of β-hydroxy esters from β-keto esters will be found in Section III,H,3.

Mixed Kolbe electrolysis of fatty acids with optically active methyl hydrogen 3-acetoxyglutarate (CLXXIV) (253) or with 3-acetoxy-3-carbethoxypropionic acid (162b) has been found possible. Since optically active β-hydroxy and α-hydroxy acids, respectively, are obtained, the difficult resolution of racemic hydroxy acids for the preparation of the optically active forms is obviated. Also of considerable interest is the possibility of directly correlating configuration and rotation. Other hydroxy acids have been formed by the Kolbe method (Section II,M).



$$CH_3(CH_2)_5COOH + HOOCCH_2\overset{\displaystyle OCOCH_3}{\overset{|}{C}}HCH_2COOCH_3 \xrightarrow[(2)\ \text{hydrolysis}]{(1)\ \text{anodic oxidation}} CH_3(CH_2)_6\overset{\displaystyle OH}{\overset{|}{C}}HCH_2COOH$$

CLXXIV (optically active)

(optically active)

The formation of vicinal dihydroxy acids by the hydroxylation of ethylenic acids by means of per acids is probably the most common and the most satisfactory method now available (*cf.* 188, 274). The triple bond is relatively resistant to the action of per acids, so that selective hydroxylation of the ethylenic unsaturation in an enynoic acid such as ximenynic acid (CLXXV) becomes possible (147, 149).

$$CH_3(CH_2)_5CH{=}CHC{\equiv}C(CH_2)_7COOH \xrightarrow{HCOOOH} CH_3(CH_2)_5CHOHCHOHC{\equiv}C(CH_2)_7COOH$$

CLXXV
Ximenynic acid

11,12-Dihydroxy-9-octadecynoic acid

An impressive work has made all the monohydroxystearic acids available (36). Most of the acids were prepared by Raney nickel hydrogenation of the corresponding keto acids, which in turn were obtained either from acetoacetic ester by acylation-deacetylation procedures (Section II,J,1) or by the dialkylcadmium method (Section II,I). 2-Hydroxystearic acid was formed by the alkaline hydrolysis of 2-bromostearic acid (*cf.* 190, 203b). 18-Hydroxystearic acid (CLXXVII) was formed by Raney nickel desulfurization and reduction of derivative CLXXVI of octadecanedioic acid.

$$HOOC(CH_2)_{16}COOCH_3 \xrightarrow[(2)\ C_2H_5SH]{(1)\ SOCl_2} C_2H_5SCO(CH_2)_{16}COOCH_3 \xrightarrow{\text{Raney Ni}} HO(CH_2)_{17}COOH$$

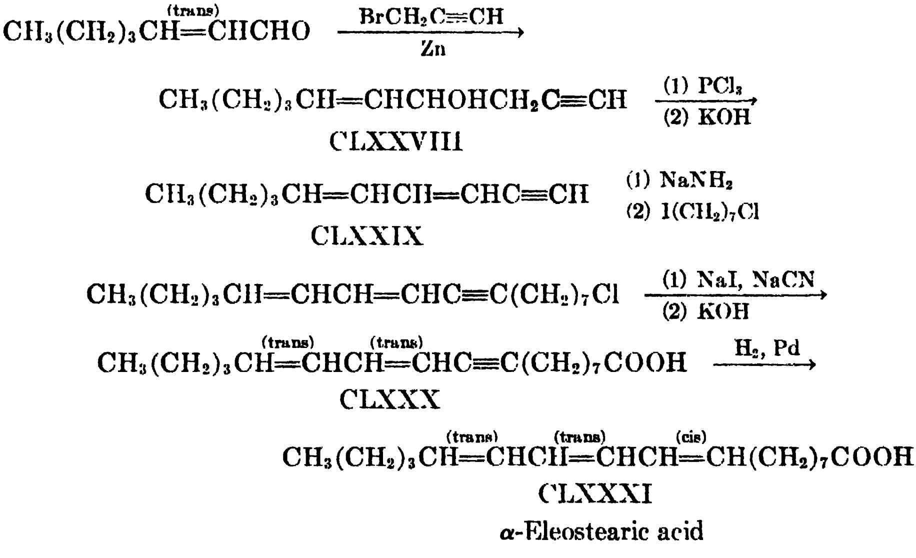
CLXXVI　　CLXXVII

The *trans* and *cis*-9,10-epoxystearic acids are available from oleic or elaidic acid, respectively, by reaction with per acids. In a reaction of unusual selectivity, hydrogenolysis over palladium in acetic acid furnishes *only* 10-hydroxystearic acid (202).

15,16-Dihydroxypalmitic acid (ustilic acid A), a fermentation product from *Ustilago zeae*, has been utilized effectively in the syntheses of several 15-keto fatty acids, as well as of 15-methylpalmitic acid. Advantage is taken of the easily oxidized vicinal dihydroxy grouping to convert the distal end of the starting material to the carboxyl group of the product (115a).

I. ELEOSTEARIC ACID AND OTHER ACIDS WITH CONJUGATED UNSATURATION

α-Eleostearic acid (*cis*-9,*trans*-11,*trans*-13-octadecatrienoic acid), from tung oil, has been synthesized as follows (112): The diunsaturated alcohol CLXXVIII was obtained from the Reformatsky condensation of *trans*-2-decenal and propargyl bromide. After a third unsaturation (as in CLXXIX) was introduced by transforming the hydroxyl group to chloride, and then dehydrochlorinating with 20 per cent alcoholic potassium hydroxide, application of the Ahmad and



$$CH_3(CH_2)_3\overset{(trans)}{CH{=}CH}CHO \xrightarrow[Zn]{BrCH_2C{\equiv}CH}$$

$$CH_3(CH_2)_3CH{=}CHCHOHCH_2C{\equiv}CH \xrightarrow[(2)\ KOH]{(1)\ PCl_3}$$

CLXXVIII

$$CH_3(CH_2)_3CH{=}CHCH{=}CHC{\equiv}CH \quad \begin{matrix}(1)\ NaNH_2\\(2)\ I(CH_2)_7Cl\end{matrix}$$

CLXXIX

$$CH_3(CH_2)_3CH{=}CHCH{=}CHC{\equiv}C(CH_2)_7Cl \xrightarrow[(2)\ KOH]{(1)\ NaI,\ NaCN}$$

$$CH_3(CH_2)_3\overset{(trans)}{CH{=}CH}\overset{(trans)}{CH{=}CH}C{\equiv}C(CH_2)_7COOH \xrightarrow{H_2,\ Pd}$$

CLXXX

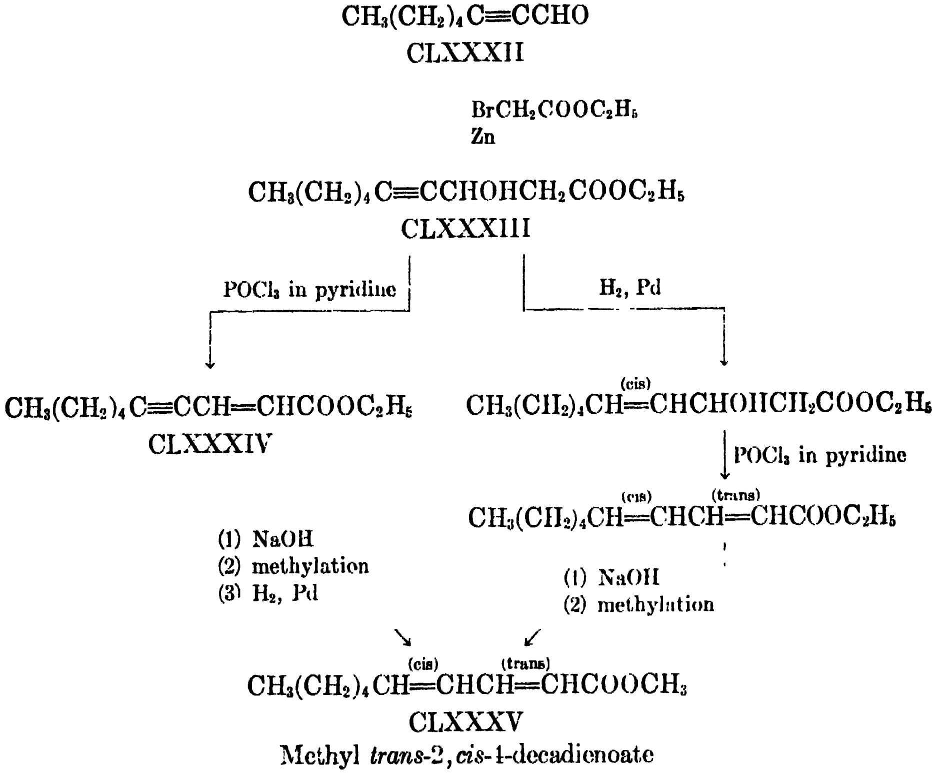
$$CH_3(CH_2)_3\overset{(trans)}{CH{=}CH}\overset{(trans)}{CH{=}CH}\overset{(cis)}{CH{=}CH}(CH_2)_7COOH$$

CLXXXI

α-Eleostearic acid

Strong reactions led to acid CLXXX. The unsaturation at position 11, generated by dehydrohalogenation, was obtained in two geometric forms. However, purification at the acid stage by clathrate formation led to homogeneous *trans*-11,*trans*-13-octadecadien-9-ynoic acid (CLXXX). Half-hydrogenation over the Lindlar catalyst gave a mixture from which, after crystallization, α-eleostearic acid (CLXXXI) could be isolated.

The conjugation in α-eleostearic acid is the result of an elimination process. Other more or less closely related processes have been reported. For example, in the synthesis of *trans*-2,*cis*-4-decadienoic methyl ester (CLXXXV), Reformatsky addition of bromoacetic ester to 2-octynal (CLXXXII) gave β-hydroxy ester CLXXXIII. Dehydration introduced a trans α,β double bond, as in CLXXXIV, and half-hydrogenation produced the conjugated 2-*trans*,4-*cis* system, as in CLXXXV. Alternately, hydrogenation of CLXXXIII before dehydration gave the expected cis ethylenic compound, which with phosphorus



$CH_3(CH_2)_4C{\equiv}CCHO$
CLXXXII

$\xrightarrow{BrCH_2COOC_2H_5,\ Zn}$

$CH_3(CH_2)_4C{\equiv}CCHOHCH_2COOC_2H_5$
CLXXXIII

$\xrightarrow{POCl_3 \text{ in pyridine}}$ $CH_3(CH_2)_4C{\equiv}CCH{=}CHCOOC_2H_5$
CLXXXIV

$\xrightarrow{H_2,\ Pd}$ $CH_3(CH_2)_4\overset{(cis)}{CH{=}}CHCHOHCH_2COOC_2H_5$

$\xrightarrow{POCl_3 \text{ in pyridine}}$ $CH_3(CH_2)_4\overset{(cis)}{CH{=}}\overset{(trans)}{CHCH{=}}CHCOOC_2H_5$

CLXXXIV: (1) NaOH (2) methylation (3) H_2, Pd

(1) NaOH (2) methylation

$CH_3(CH_2)_4\overset{(cis)}{CH{=}}\overset{(trans)}{CHCH{=}}CHCOOCH_3$
CLXXXV
Methyl *trans*-2,*cis*-4-decadienoate

oxychloride in pyridine was dehydrated to the 2-*trans*,4-*cis* compound containing appreciable amounts of the 2-*trans*,4-*trans* isomer (104).

Methyl ricinstearolate (CLXXXVI) reacts with phosphorus oxychloride or with thionyl chloride to yield the corresponding chloro compound. This with

$$\underset{\text{CLXXXVI}}{CH_3(CH_2)_4CHOHCH_2C{\equiv}C(CH_2)_7COOCH_3} \xrightarrow[\text{(2) quinoline}]{\text{(1) POCl}_3\text{ in pyridine}}$$

$$\underset{\substack{\text{CLXXXVII}\\ \text{Methyl ximenynate}}}{CH_3(CH_2)_4CH{=}CHC{\equiv}C(CH_2)_7COOCH_3} + \cdots$$

boiling quinoline or with alcoholic potassium hydroxide gave a mixture containing approximately 75 per cent of the conjugated ene-yne compound CLXXXVII, which proved to be the same as methyl ximenynate (113, 147). Castor oil or methyl ricinoleate treated first with thionyl chloride and then with alcoholic potassium hydroxide gives *trans*-9,*trans*-11-octadecadienoic derivatives, geometric isomerization occurring as well as dehydrochlorination (147). Direct dehydration of the ricinoleic compounds produces more than twice as much nonconjugated product as conjugated product (228). Allylic bromination of ethylenic and acetylenic acids with *N*-bromosuccinimide followed by dehydrobromination gives mixtures from which acids containing conjugated unsaturation can be isolated (204, 216; also *cf.* Section II,O,1).

Two of the four possible isomers of 3,5-tridecadienoic acid were prepared according to the accompanying formulations (92). Here, nonynylmagnesium bromide with acrolein gave carbinol CLXXXVIII. This carbinol when treated first with phosphorus tribromide and then with cuprous cyanide formed the thirteen-carbon nitrile, which was converted to the methyl ester of *trans*-3-tridecen-5-ynoic acid (CLXXXIX). Half-hydrogenation over the Lindlar catalyst furnished the desired conjugated ester, methyl *trans*-3,*cis*-5-tridecadienoate (CXC). The *trans*-3,*trans*-5 form was obtained by isomerization with iodine and light. Other conjugated systems have been synthesized in a related manner (e.g., 45, 159; also *cf.* Sections II,A and II,B).

$$CH_3(CH_2)_6C{\equiv}CMgBr \xrightarrow{CH_2{=}CHCHO}$$

$$\underset{\text{CLXXXVIII}}{CH_3(CH_2)_6C{\equiv}CCHOHCH{=}CH_2} \xrightarrow{PBr_3}$$

$$CH_3(CH_2)_6C{\equiv}CCH\overset{(\text{trans})}{=}CHCH_2Br \xrightarrow[(2)\ CH_3OH\ +\ HCl(H_2O)]{(1)\ CuCN}$$

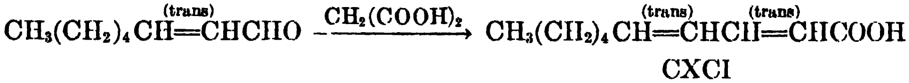
$$\underset{\text{CLXXXIX}}{CH_3(CH_2)_6C{\equiv}CCH{=}CHCH_2COOCH_3} \xrightarrow{H_2,\ Pd}$$

$$\underset{\text{CXC}}{CH_3(CH_2)_6CH\overset{(\text{cis})}{=}CHCH\overset{(\text{trans})}{=}CHCH_2COOCH_3}$$

Methyl *trans*-3,*cis*-5-tridecadienoate

The conversion of conjugated ene-ynes, such as CLXXX, CLXXXIV, and CLXXXIX, to conjugated dienes by half-hydrogenation appears to be a useful general method, although both stereospecificity and selectivity may be poor. Other examples of such half-hydrogenations, as well as half-hydrogenations of conjugated diynes, are available. Thus ximenynic acid (CLXXXVII) with one mole of hydrogen yielded *cis*-9,*trans*-11-octadienoic acid (149); methyl 2,4-decadiynoate with two moles of hydrogen yielded methyl *cis*-2,*cis*-4-decadienoate (104; but see 7); and 9,11-octadecadiynoic acid with two moles of hydrogen yielded *cis*-9,*cis*-11-octadecadienoic acid (7). The last acid could be isomerized with iodine to the cis,trans and then to the trans,trans form. In contrast to these successful hydrogenation experiments, all of which made use of the Lindlar catalyst, 10,12-docosadiynedioic dimethyl ester over Raney nickel at 100°C. failed to yield significant amounts of conjugated ene-yne or diene (240).

A different method develops conjugated unsaturation by combining an α,β-unsaturated aldehyde with malonic acid in the presence of pyridine (Doebner condensation). For example, *trans*-2-octenal leads to *trans*-2,*trans*-4-decadienoic acid (CXCI) (104; also *cf.* 114, 174).

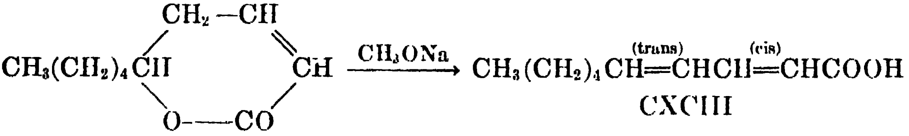


$$CH_3(CH_2)_4\overset{(trans)}{CH}{=}CHCHO \xrightarrow{CH_2(COOH)_2} CH_3(CH_2)_4\overset{(trans)}{CH}{=}CHCH{=}\overset{(trans)}{C}HCOOH$$

CXCI

trans-2,*trans*-4-Decadienoic acid

Other preparations of fatty acids incorporating conjugated unsaturation include extending the carbon chain of sorbic acid (*trans*-2,*trans*-4-hexadienoic acid) by standard steps to a longer acid, such as all-*trans*-2,6,8-decatrienoic acid (175; *cf.* Section III,C) and opening an unsaturated lactone ring with methoxide, e.g., CXCII to CXCIII (104, 125). The many reaction schemes leading to vitamin A or to carotenes (*cf.* Section III,G) present a wealth of suggestions for the means of introducing conjugated unsaturation. The Wittig-Geissler reaction (Section II,N) is readily adaptable to the production of conjugated unsaturation. The synthesis of cortisalin, isolated from *Corticium salicinum* Bres., shows another useful way of building a conjugated system (203a).



$$\xrightarrow{CH_3ONa} CH_3(CH_2)_4\overset{(trans)}{CH}{=}CHCH{=}\overset{(cis)}{C}HCOOH$$

CXCIII

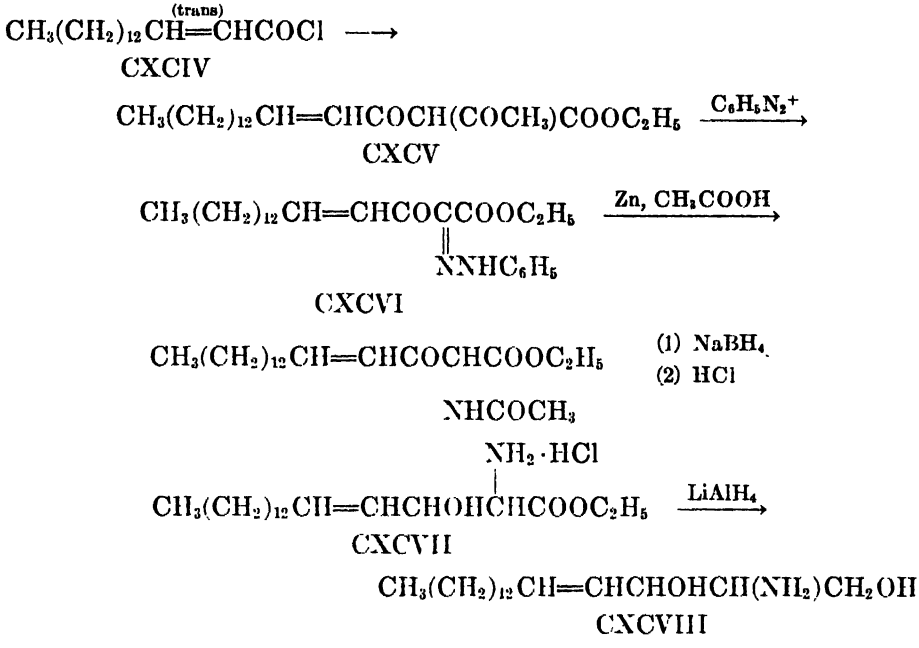
CXCII

Strong alkali is known to convert skipped unsaturation, as in linoleic or linolenic acids, to conjugated unsaturation. Conditions making use of potassium *tert*-butoxide at temperatures no higher than 99°C. have been found to be particularly suitable in this isomerization (117). Although stillingic acid (*trans*-2,*cis*-4-decadienoic acid) is stable to boiling dilute potassium hydroxide, isomerization over potassium hydroxide does occur in ethylene glycol at 170–180°C. (115). The major product still retains the conjugated diene system but, interestingly enough, the unsaturation is displaced away from the carboxylic acid group.

Conjugated diacetylenic unsaturation has been introduced by Glaser coupling (Section II,L) as well as by other methods summarized elsewhere (232).

J. SPHINGOSINE

Sphingosine (*trans-erythro*-1,3-dihydroxy-2-amino-4-octadecene), although an amine, is classed as a lipide material. Dihydrosphingosine, the corresponding saturated compound, has been synthesized (*cf.* 4, 66, 67, 68, 176, 244, 245, 254), as has sphingosine itself (254). The synthesis of the latter proceeded from *trans*-2-hexadecenoic acid, which in the form of the acid chloride (CXCIV) was combined with acetoacetic ester to give CXCV. Phenyldiazonium coupling effected deacetylation and furnished the phenylhydrazone CXCVI. Reduction of the hydrazone group by zinc followed by reduction of the keto group by means of sodium borohydride gave a mixture of diastereoisomers which could be separated. Deacetylation of the erythro form with hydrochloric acid gave the hydrochloride of the aminoalcohol ester CXCVII, and finally reduction with lithium aluminum hydride gave racemic sphingosine (CXCVIII).



$$CH_3(CH_2)_{12}\overset{\text{(trans)}}{CH}{=}CHCOCl \longrightarrow$$

CXCIV

$$CH_3(CH_2)_{12}CH{=}CHCOCH(COCH_3)COOC_2H_5 \xrightarrow{C_6H_5N_2^+}$$

CXCV

$$CH_3(CH_2)_{12}CH{=}CHCO\underset{\underset{NNHC_6H_5}{\|}}{C}COOC_2H_5 \xrightarrow{Zn,\ CH_3COOH}$$

CXCVI

$$CH_3(CH_2)_{12}CH{=}CHCO\underset{NHCOCH_3}{CH}COOC_2H_5 \quad \begin{array}{l}(1)\ NaBH_4\\(2)\ HCl\end{array}$$

$$CH_3(CH_2)_{12}CH{=}CHCHOH\overset{\overset{NH_2\cdot HCl}{|}}{C}HCOOC_2H_5 \xrightarrow{LiAlH_4}$$

CXCVII

$$CH_3(CH_2)_{12}CH{=}CHCHOHCH(NH_2)CH_2OH$$

CXCVIII

DL-Sphingosine

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V. Appendix (Added in Proof)

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ARTIFICIAL ESTROGENS

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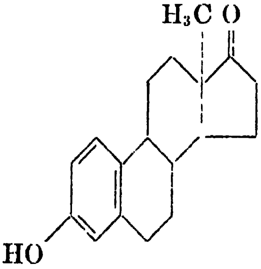
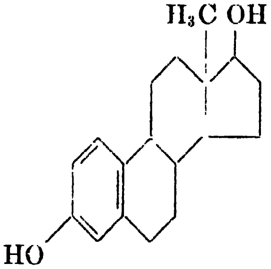
I. INTRODUCTION

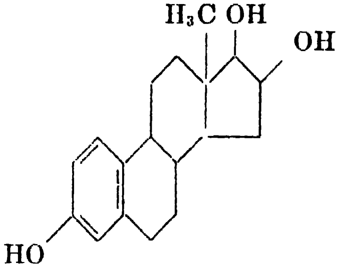
The lack of molecular specificity in the series of natural estrogens estrone (I), "α"-estradiol (II), estriol (III), equilenin (IV), and equilin (V) led Dodds and his colleagues, about 1930, to examine how the molecule of a natural estrogen might be changed without destroying estrogenic activity. This work culminated in 1938 in the discovery of the estrogenically potent synthetic compounds diethylstilbestrol (VI) (100), hexestrol (VII) (53), and dienestrol (VIII) (101). These compounds remain the most potent, useful estrogens of the stilbene type. These results of the workers at the Courtauld Institute had immediate importance in estrogen therapy, since previously only natural products had been available and their administration necessitated injection. The synthetic compounds were found to possess all the qualitative estrogenic properties of the



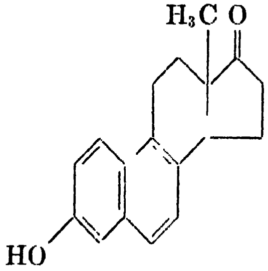
I
Estrone



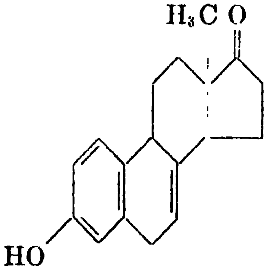
II
"α"-Estradiol



III
Estriol

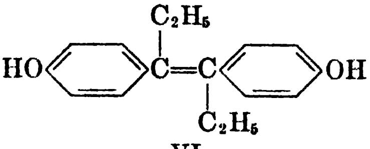


IV
Equilenin



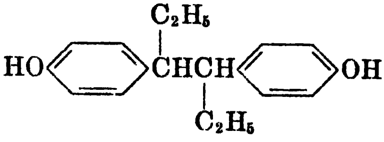
V
Equilin

natural estrogens, were cheap to produce, and were active by mouth. They have attained considerable clinical importance (187).



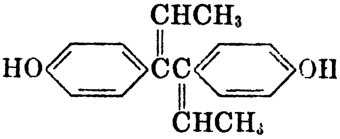
VI

Diethylstilbestrol



VII

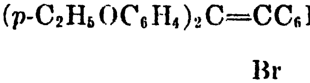
Hexestrol



VIII

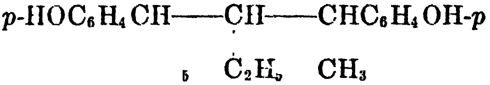
Dienestrol

Stemming from the classical work of Lacassagne (250) and Huggins (196)' the study of estrogens in their relation to cancer has become a field of some extent (42), and diethylstilbestrol has found a place in prostatic cancer therapy. The stimulus of the early successes has led to the preparation and biological testing of a vast number of compounds more or less closely related to the three stilbene-type estrogens. Although few have attained practical significance, this work has provided valuable data on chemical constitution and estrogenic activity. The syntheses of the triphenylethylenes by Robson and coworkers (363, 364, 365), of 1,1-bis(p-ethoxyphenyl)-2-bromo-2-phenylethylene (IX), which



$(p\text{-}C_2H_5OC_6H_4)_2C{=}\underset{Br}{C}C_6H_5$

IX



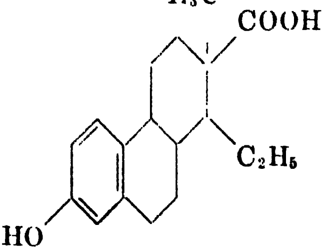
$p\text{-}HOC_6H_4CH{-}\underset{C_2H_5}{CH}{-}\underset{CH_3}{CH}C_6H_4OH\text{-}p$

X

Benzestrol

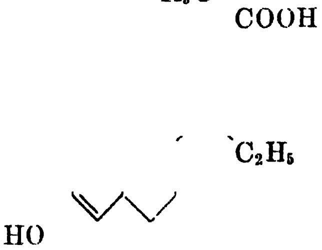
has clinical use, and of benzestrol (X) by Blanchard, Stuart, and Tallman (25) were notable discoveries.

In 1944 the elaboration of some earlier observations was initiated by Miescher and coworkers in Switzerland (285). This work led to the discovery of an entirely



XI

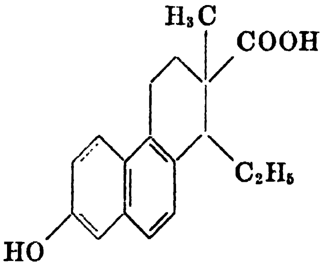
Doisynolic acid



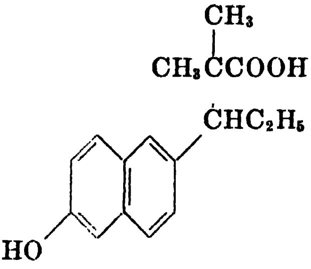
XII

Monodehydrodoisynolic acid

new type of estrogen, closely related to the natural hormones. Doisynolic acid (XI), monodehydrodoisynolic acid (XII), and bisdehydrodoisynolic acid (XIII) are examples of these highly potent estrogens.

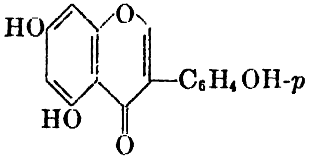


XIII
Bisdehydrodoisynolic acid



XIV
Horeau acid

Structural simplification in this series was achieved by the discovery of the allenolic acids in 1947 by Horeau and Jacques (186). Horeau acid (XIV) is an example of this class of estrogen. More recently, in 1951, Bradbury and White (31) discovered the estrogenic activity of isoflavones such as genistein (XV).



XV
Genistein

While work is yet at an early stage, it would seem that these compounds are heterocyclic ring-closed analogs of the stilbene type of estrogen. Nonnatural estrogens have previously been referred to as synthetic estrogens, but in view of the recent total syntheses of the natural products and in accordance with a suggestion due to Horeau (185), the preferable title "artificial estrogens" has been used.

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Throughout this review the estrogenically more active *trans*-diethylstilbestrol is referred to simply as diethylstilbestrol; this name is now generally preferred to the shortened form, stilbestrol. The more potent *meso*-hexestrol is similarly referred to as hexestrol. Of the three dienestrols, the more active isomer is referred to as dienestrol or α-dienestrol (252).

The subject has been taken up from the termination of Solmssen's review (451) and covers *Chemical Abstracts* from 1946 to 1955, inclusive; earlier work has occasionally been referred to for purposes of continuity. All compounds related to diethylstilbestrol, hexestrol, or dienestrol have been included. Other reviews (62, 68, 84, 137, 208, 230, 255, 279, 328, 329, 330, 331, 332, 333, 334, 335) of chemical interest have appeared during the period.

The estrogenic acids and estrogenic heterocyclic compounds have been omitted, since they have as yet made a smaller contribution to the understanding of the molecular features associated with estrogenic activity. Various miscellaneous compounds have also been omitted. Because of the extensive published work it has not been possible to discuss the relationship of estrogens to cancer or the analytical chemistry of estrogens. The nomenclature used is that of *Chemical Abstracts*.

II. SYNTHESES OF DIETHYLSTILBESTROL, HEXESTROL, AND DIENESTROL

Much of the more recent synthetic work directed specifically to the three principal artificial estrogens has been based on earlier methods (445, 446, 447). However, some novel modifications and new syntheses have been introduced, and some aspects of reaction mechanisms have been investigated.

A. SYNTHESES OF DIETHYLSTILBESTROL

1. *Modifications of the Dodds synthesis*

The original synthesis of Dodds, Golberg, Lawson, and Robinson (100) involved the following steps:

$$p\text{-}CH_3OC_6H_4CHO \xrightarrow{KCN}$$

Anisaldehyde

$$p\text{-}CH_3OC_6H_4CHOHCOC_6H_4OCH_3\text{-}p \xrightarrow[100°C.,\ 24\ hr.]{Zn\ dust,\ CH_3COOH}$$

Anisoin

$$p\text{-}CH_3OC_6H_4CH_2COC_6H_4OCH_3\text{-}p \quad \begin{matrix}C_2H_5ONa\\ C_2H_5I\end{matrix}$$

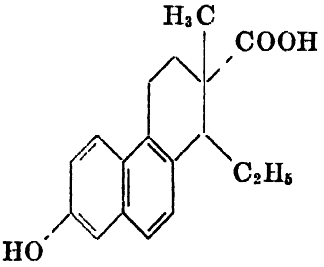
Desoxyanisoin

$$p\text{-}CH_3OC_6H_4CH(C_2H_5)COC_6H_4OCH_3\text{-}p \xrightarrow{C_2H_5MgBr}$$

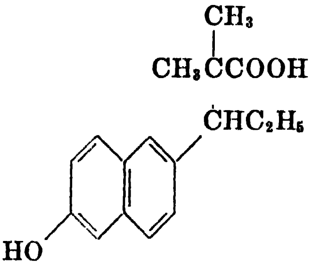
XVI

α-Ethyldesoxyanisoin

new type of estrogen, closely related to the natural hormones. Doisynolic acid (XI), monodehydrodoisynolic acid (XII), and bisdehydrodoisynolic acid (XIII) are examples of these highly potent estrogens.

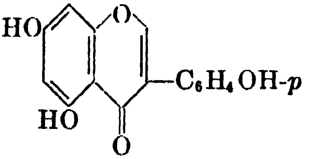


XIII
Bisdehydrodoisynolic acid



XIV
Horeau acid

Structural simplification in this series was achieved by the discovery of the allenolic acids in 1947 by Horeau and Jacques (186). Horeau acid (XIV) is an example of this class of estrogen. More recently, in 1951, Bradbury and White (31) discovered the estrogenic activity of isoflavones such as genistein (XV).



XV
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Anisaldehyde

$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CHOHCOC}_6\text{H}_4\text{OCH}_3\text{-}p \xrightarrow[\text{100°C., 24 hr.}]{\text{Zn dust, CH}_3\text{COOH}}$

Anisoin

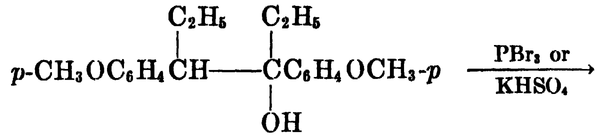
$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{COC}_6\text{H}_4\text{OCH}_3\text{-}p \xrightarrow[\text{C}_2\text{H}_5\text{I}]{\text{C}_2\text{H}_5\text{ONa}}$

Desoxyanisoin

$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH(C}_2\text{H}_5\text{)COC}_6\text{H}_4\text{OCH}_3\text{-}p \xrightarrow{\text{C}_2\text{H}_5\text{MgBr}}$

XVI

α-Ethyldesoxyanisoin



$$p\text{-}CH_3OC_6H_4\underset{}{\overset{C_2H_5}{\overset{|}{C}}}H\text{——}\underset{\underset{OH}{|}}{\overset{C_2H_5}{\overset{|}{C}}}C_6H_4OCH_3\text{-}p \xrightarrow[KHSO_4]{PBr_3\text{ or}}$$

XVII

3,4-Bis(*p*-methoxyphenyl)-3-hexanol

$$p\text{-}CH_3OC_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_4OCH_3\text{-}p \xrightarrow[C_2H_5OH]{KOH}$$

XVIII

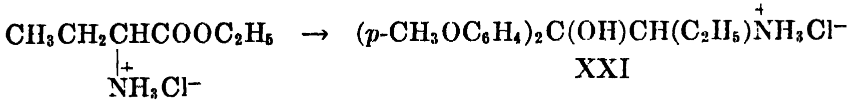
Diethylstilbestrol dimethyl ether

$$p\text{-}HOC_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_4OH\text{-}p$$

XIX

Diethylstilbestrol

In this and related syntheses (369, 550) α-ethyldesoxyanisoin (XVI) is the key intermediate. Wilder Smith (418) obtained this intermediate in good yield by a novel route: the hydrochloride of ethyl α-aminobutyrate (XX) was reacted with *p*-methoxyphenylmagnesium bromide to give the hydrochloride of 2-amino-1,1-bis(*p*-methoxyphenyl)-1-butanol (XXI) in 64 per cent yield. Conversion of



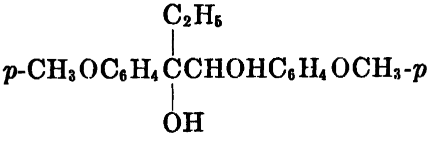
$$CH_3CH_2\underset{\underset{\overset{+}{N}H_3Cl^-}{|}}{C}HCOOC_2H_5 \rightarrow (p\text{-}CH_3OC_6H_4)_2C(OH)CH(C_2H_5)\overset{+}{N}H_3Cl^-$$

XX

XXI

XXI to the free base, in 92 per cent yield, followed by pinacolic deamination with nitrous acid (269, 270, 271, 506), gave α-ethyldesoxyanisoin in 90 per cent yield. Variation of the α-aminoester hydrochloride and the Grignard reagent should permit the synthesis of a variety of substituted stilbenes by this method.

Kuwada and Sasagawa (247) obtained α-ethyldesoxyanisoin by acid rearrangement of the pinacol 3,4-bis(*p*-methoxyphenyl)-3,4-butanediol (XXII), the latter being prepared by the interaction of anisoin and ethylmagnesium

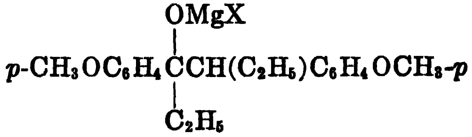


$$p\text{-}CH_3OC_6H_4\underset{\underset{OH}{|}}{\overset{C_2H_5}{\overset{|}{C}}}CHOHC_6H_4OCH_3\text{-}p$$

XXII

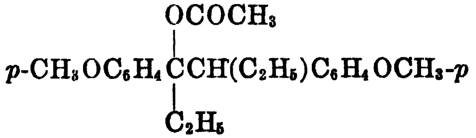
iodide. Sah (374), however, could not substantiate the yields claimed by Kuwada and Sasagawa and introduced slight modifications of the conditions in the overall synthesis of diethylstilbestrol. It was found better to carry out the dehydration step to XVIII by phosphorus pentoxide, and the final demethylation was done with aluminum bromide at 120°C.

Schwarzkopf (389) introduced the improvement of omitting the isolation of the carbinol XVII; instead, the Grignard reaction product (XXIII) was converted directly to XVIII by heating with an excess of an inorganic or organic acid chloride or anhydride. Esters such as the acetate of 3,4-bis(*p*-methoxyphenyl)-3-hexanol (XXIV) could be isolated and were considered to be the reaction intermediates. XXIV eliminates acetic acid on heating or even on standing to give the stilbene; acetyl chloride with XXIII gives a 72 per cent yield of diethylstilbestrol dimethyl ether. In a second synthesis, Schwarzkopf (390) obtained XXIII from 3-(*p*-methoxyphenyl)-3-propanone and the Grignard reagent from 2-bromo-3-(*p*-methoxyphenyl)propane; the product was dehydrated to diethylstilbestrol dimethyl ether by distillation at 170°C. at 0.4 mm. pressure after removal of the solvent. Takahashi (489) used a similar method and obtained diethylstilbestrol directly from α-ethyldesoxyanisoin by the action of ethylmagnesium iodide, followed by removal of the solvent and heating at 165–170°C.



$$p\text{-}CH_3OC_6H_4\underset{C_2H_5}{\overset{OMgX}{C}}CH(C_2H_5)C_6H_4OCH_3\text{-}p$$

XXIII



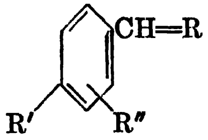
$$p\text{-}CH_3OC_6H_4\underset{C_2H_5}{\overset{OCOCH_3}{C}}CH(C_2H_5)C_6H_4OCH_3\text{-}p$$

XXIV

Rabald and Kraus (345) improved the yields of diethylstilbestrol in the Dodds type of synthesis by triturating residues from the dehydration step with a little iodine; the asymmetric alkenes are thereby isomerized to the stilbene. In the course of other work Hofstetter and Wilder Smith (183) dehydrated a mixture of 3,4-bis(*p*-methoxyphenyl)-2-hexanol and the 1-hexanol with an acetyl chloride–acetic anhydride mixture and isomerized the product with iodine in toluene to obtain diethylstilbestrol dimethyl ether.

2. Syntheses from anethole

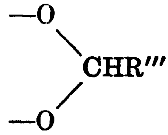
Kharasch (233) exemplified the extension of the Kharasch–Kleiman synthesis of diethylstilbestrol (237). Starting materials of the type shown in formula XXV



XXV

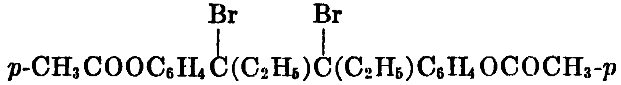
R = alkylidene group of two to six carbon atoms
R′ = alkoxy group of one to four carbon atoms

R'' = hydrogen or alkoxy group of one to four carbon atoms
R' and R'' may be united, e.g.,



R''' = alkyl group of one to four carbon atoms

may be used. Treatment with gaseous hydrogen bromide at −10° to −20°C. yielded the α-bromo compound, which with sodium amide in liquid ammonia gave the stilbene. Bowman (30) dehydrohalogenated benzyl chloride to stilbene, using a complex prepared by heating magnesium and iodine together. Turnbull (510, 511) treated 3,4-bis(*p*-acetoxyphenyl)-3,4-dibromohexane (XXVI), ob-



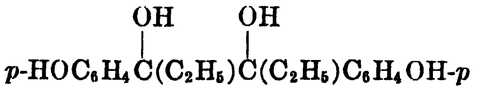
$$p\text{-}CH_3COOC_6H_4\overset{\overset{\text{Br}}{|}}{C}(C_2H_5)\overset{\overset{\text{Br}}{|}}{C}(C_2H_5)C_6H_4OCOCH_3\text{-}p$$

XXVI

tained by brominating diethylstilbestrol or hexestrol, with zinc dust in alcohol and obtained a product melting at 141–142°C. This product was considered identical to one previously obtained by Dodds, Golberg, Lawson, and Robinson (102) and later shown by Walton and Brownlee (533) to be a eutectic made up of 60 per cent of ψ-diethylstilbestrol and 40 per cent of the trans isomer. Turnbull (510, 511) found that treatment of the eutectic with acetic anhydride in pyridine gave the diacetate of *cis*-diethylstilbestrol.

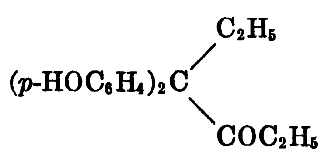
3. Syntheses involving pinacol–pinacolone and retropinacolone rearrangements

Adler, Gie, and v. Euler (3) improved previous syntheses of this type (448) by using unprotected *p*-hydroxypropiophenone as the starting material and reducing it with sodium amalgam in alkaline solution instead of the usual amalgamated aluminum. By this method they obtained the higher-melting form, m.p. 215–217°C., of the pinacol 3,4-bis(*p*-hydroxyphenyl)-3,4-hexanediol (XXVII) in 95 per cent yield. Rearrangement of XXVII in ether solution by

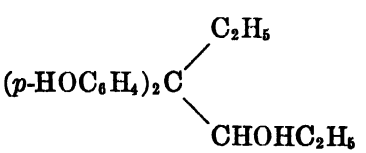


$$p\text{-}HOC_6H_4\overset{\overset{\text{OH}}{|}}{C}(C_2H_5)\overset{\overset{\text{OH}}{|}}{C}(C_2H_5)C_6H_4OH\text{-}p$$

XXVII



XXVIII



XIX

gaseous hydrogen chloride gave the pinacolone 3,3-bis(*p*-hydroxyphenyl)-4-hexanone (XXVIII) quantitatively (501, 502). Reduction of XXVIII with sodium in amyl alcohol at 140°C. gave a 95 per cent yield of the pinacolone alcohol, 3,3-bis(*p*-hydroxyphenyl)-4-hexanol (XXIX), and finally retropinacolone rearrangement of this carbinol resulted in a 68 per cent overall yield of diethylstilbestrol. Contrary to these results, Shishido and Nozaki (398) found that pinacolic reduction of phenolic ketones or their esters does not proceed well; however, they used amalgamated aluminum. Using *p*-methoxypropiophenone, Shishido and Nozaki obtained a mixture of pinacols of the type shown in formula XXVII and by sulfuric acid rearrangement of the mixture obtained the pinacolone in 54 per cent overall yield. The pinacolone alcohol, obtained by reducing the pinacolone with sodium in xylene at 140°C., could not be satisfactorily rearranged with sulfuric acid, but iodine in chloroform (547) gave diethylstilbestrol dimethyl ether in 14 per cent overall yield. Demethylation to diethylstilbestrol was accomplished by treating the dimethyl ether with an ethereal solution of methylmagnesium iodide, evaporating the solvent, and heating the residue at 170°C. (248, 467).

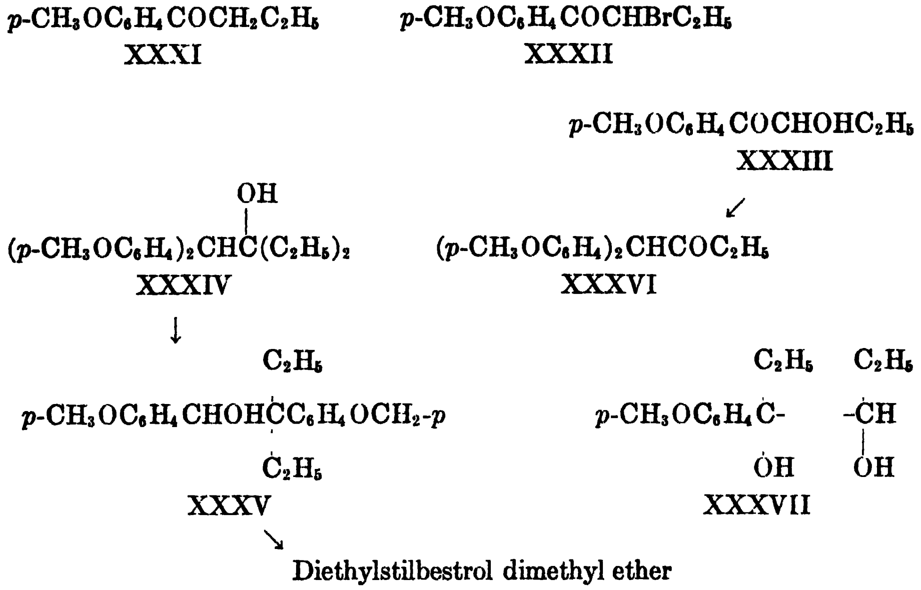
In this type of synthesis 3,3-bis(*p*-hydroxyphenyl)-4-hexanone (XXVIII) may be considered the key intermediate. Various routes for its preparation were investigated by Shishido, Nozaki, and Kurihara (406). First, in a synthesis of the diacetate of XXVIII on the basis of their earlier work (404) they reacted phenol and bipropionyl in acetic acid–sulfuric acid and obtained a 19 per cent yield of 3,3-bis(*p*-acetoxyphenyl)-4-hexanone. A second method involved the ethylation of 1,1-bis(*p*-methoxyphenyl)acetonitrile (XXX) by ethyl iodide and sodium amide, followed by conversion of the 1,1-bis(*p*-methoxyphenyl)-butyronitrile obtained to 3,3-bis(*p*-methoxyphenyl)-4-hexanone by reaction

$$(p\text{-}CH_3OC_6H_4)_2\,CHCN$$

XXX

with ethylmagnesium bromide. Reduction and retropinacolone rearrangement then gave diethylstilbestrol dimethyl ether in 20 per cent yield on the basis of the butyronitrile. The action of five moles of the Grignard reagent on the butyronitrile at 130–170°C. also effected demethylation to give 3,3-bis(*p*-hydroxyphenyl)-4-hexanone, which could be converted to diethylstilbestrol. In a third method a Grignard reagent replaced sodium amide as the condensing agent; thus XXX was treated with ethylmagnesium iodide and ethyl iodide to give a 24 per cent yield of 3,3-bis(*p*-methoxyphenyl)-4-hexanone. This type of reaction had been used previously in other connections (135, 157, 538).

In a synthesis developed by Peteri (340) 1,1-bis(*p*-methoxyphenyl)-2-ethyl-2-butanol (XXXIV) was converted by phosphorus trichloride in toluene into diethylstilbestrol dimethyl ether, the reaction presumably proceeding via the intermediate XXXV. Tanabe, Onishi, and Takamura (500) converted *p*-methoxybutyrophenone (XXXI) into the α-bromo compound (XXXII) by treatment with bromine in acetic acid below 20°C. Hydrolysis with sodium carbonate solution after treatment of XXXII with potassium acetate gave the carbinol (XXXIII), which on reaction with anisole in the presence of sulfuric acid gave 1,1-bis(*p*-methoxyphenyl)-2-butanone (XXXVI). The latter with ethylmag-



$p\text{-}CH_3OC_6H_4COCH_2C_2H_5$ XXXI

$p\text{-}CH_3OC_6H_4COCHBrC_2H_5$ XXXII

$p\text{-}CH_3OC_6H_4COCHOHC_2H_5$ XXXIII

$(p\text{-}CH_3OC_6H_4)_2CH\overset{OH}{C}(C_2H_5)_2$ XXXIV

$p\text{-}CH_3OC_6H_4CHOH\underset{C_2H_5}{\overset{C_2H_5}{C}}C_6H_4OCH_3\text{-}p$ XXXV

$(p\text{-}CH_3OC_6H_4)_2CHCOC_2H_5$ XXXVI

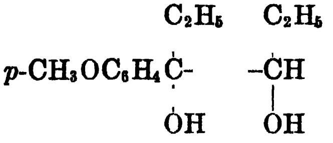
$p\text{-}CH_3OC_6H_4\underset{OH}{\overset{C_2H_5}{C}}\text{-}\underset{OH}{\overset{C_2H_5}{CH}}$ XXXVII

Diethylstilbestrol dimethyl ether

nesium bromide yielded XXXIV. Alternatively, XXXIII was converted to 3-(*p*-methoxyphenyl)-3,4-hexanediol (XXXVII) by ethylmagnesium bromide. Reaction of XXXVII with anisole in sulfuric acid at 30°C. gave diethylstilbestrol dimethyl ether. Yoshida and Akagi (559) obtained XXXIII by the same method but converted it into XXXVI by reaction with *p*-methoxyphenylmagnesium bromide, followed by dehydration of the 1,1-bis(*p*-methoxyphenyl)-1,2-butanediol obtained. Diethylstilbestrol dimethyl ether was then obtained via XXXIV as indicated.

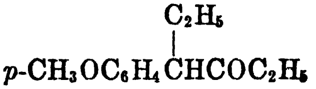
4. Introduction of the anisyl group by a Grignard reaction

Three syntheses of this type have been developed (126, 249, 547). The intermediate was 3-(*p*-methoxyphenyl)-4-hexanone (XXXIX), obtained by acid rearrangement of 3-(*p*-methoxyphenyl)-3,4-hexanediol (XXXVIII).



$p\text{-}CH_3OC_6H_4\underset{OH}{\overset{C_2H_5}{C}}\text{-}\underset{OH}{\overset{C_2H_5}{CH}}$

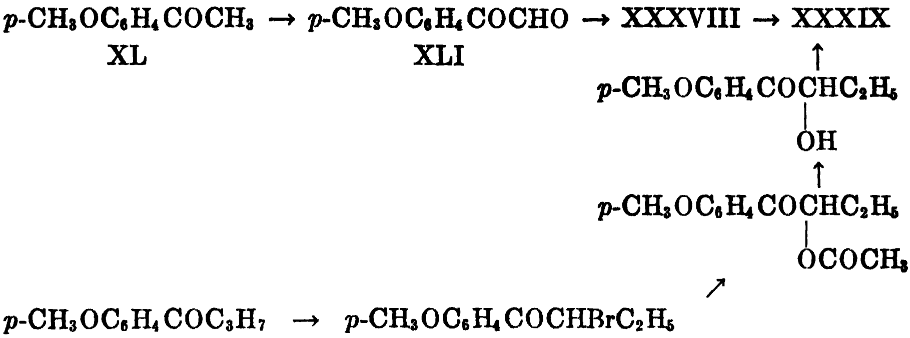
XXXVIII



$p\text{-}CH_3OC_6H_4\overset{C_2H_5}{CH}COC_2H_5$

XXXIX

Treatment of XXXIX with *p*-methoxyphenylmagnesium bromide followed by dehydration and demethylation yielded diethylstilbestrol. Shishido and Nozaki (400) developed two new routes to the intermediate ketone (XXXIX). In one method *p*-methoxyacetophenone (XL) was converted in improved yield (7, 227) into *p*-methoxyphenylglyoxal (XLI) by selenium dioxide oxidation; subsequent reaction with ethylmagnesium iodide gave XXXIX via the diol (XXXVIII).



$$\begin{tikzcd}
\underset{\text{XL}}{p\text{-}CH_3OC_6H_4COCH_3} \arrow[r] & \underset{\text{XLI}}{p\text{-}CH_3OC_6H_4COCHO} \arrow[r] & \text{XXXVIII} \arrow[r] & \text{XXXIX} \\
 & & & p\text{-}CH_3OC_6H_4CO\underset{\displaystyle OH}{\underset{|}{C}}HC_2H_5 \arrow[u] \\
 & & & p\text{-}CH_3OC_6H_4CO\underset{\displaystyle OCOCH_3}{\underset{|}{C}}HC_2H_5 \arrow[u] \\
p\text{-}CH_3OC_6H_4COC_3H_7 \arrow[r] & p\text{-}CH_3OC_6H_4COCHBrC_2H_5 \arrow[rru] & &
\end{tikzcd}$$

The second series of reactions used were essentially the same as those previously described for converting a ketone into its α-hydroxy derivative (500, 559). The diol (XXXVIII) obtained in both these methods was the new β-form (m.p. 99-100°C.); the diastereoisomeric α-form (m.p. 83–84°C.) had been obtained in the previous syntheses of this type.

5. Other methods

Rubin and Wishinsky (370) obtained a 4-amino-4′-hydroxy-α,α′-diethylstilbene, m.p. 155–156°C. Weiss (541) carefully purified the crude material obtained by these workers and obtained an isomer, m.p. 180–183°C., which by the diazo reaction yielded diethylstilbestrol. It was concluded that the isomer melting at 155–156°C. was the cis form and the higher-melting isomer the trans form.

According to a Hungarian patent (350) *p*-methoxypropiophenone hydrazone when shaken in petroleum ether with mercuric oxide gave a solution of (*p*-methoxyphenyl)ethyldiazomethane. Treatment of this solution with gaseous sulfur dioxide gave an inseparable mixture of 1,2-bis(*p*-methoxyphenyl-1,2-diethylethylene sulfone and *p*-methoxypropiophenone azine. The mixture was melted to decompose the sulfone; fractional crystallization of the solid residue yielded diethylstilbestrol dimethyl ether.

B. SYNTHESES OF HEXESTROL

1. Wurtz-type syntheses

A Wurtz-type coupling of two molecules of a *p*-(α-halopropyl)anisole has been the method used in some previous hexestrol syntheses devised by Peak and Short (337), Docken and Spielman (96), and Bernstein and Wallis (17). These methods used alkali or alkaline earth metals in anhydrous organic media as the coupling agents. Kharasch and Kleiman (236) used the same starting materials but effected coupling by the cobaltous chloride–Grignard reagent method.

Shishido and Nozaki (399, 402), employing an earlier reaction due to Ogata and Oda (319), heated anethole hydrobromide (XLII) or hydrochloride in

$p\text{-}CH_3OC_6H_4CHBrC_2H_5$
XLII

$p\text{-}HOC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4OH\text{-}p$
XLIII

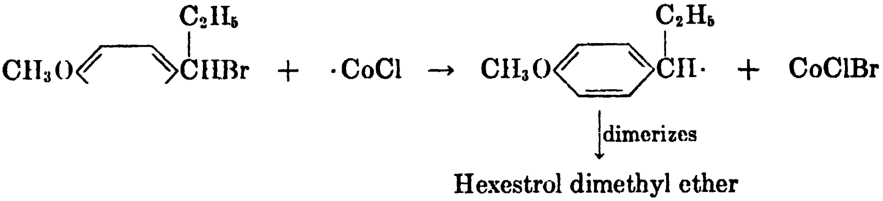
ligroin with water and iron powder and obtained hexestrol dimethyl ether in 10–15 per cent yields. The method avoids the anhydrous media or low temperatures used in previous methods and has the advantage that the presence of water stabilizes the halide starting materials (344). Hexestrol dimethyl ether was demethylated to hexestrol (XLIII) by the Grignard method. Later Shishido and Nozaki (403) improved and generalized their synthesis by using reduced iron as the coupling agent. By this method anethole hydrobromide in toluene solution gave a 20 per cent yield of hexestrol dimethyl ether; the hydrochloride gave only a 14–15 per cent yield. Buu-Hoï and Hoán (48) also used reduced iron in a similar procedure and recorded an overall yield from anethole of 40 per cent of a mixture of hexestrol dimethyl ethers. The mixture contained about equal amounts of the meso and racemic ethers. It was further found that the ratio of the meso to the racemic form depended on the metal used for coupling. With reduced iron powder, Raney alloy, or Raney nickel high yields of the meso form were obtained, but with Devarda's alloy, zinc dust, the zinc–copper couple, or magnesium, much of the racemic form was obtained; with reduced copper a high yield of the racemic form, as sole product, was produced.

Girard and Sandulesco (142) converted anethole hydrobromide to hexestrol dimethyl ether, using powdered sodium or sodium strips (143) in benzene below 48°C. Schoeller, Inhoffen, Steinruck, and Hoss (385) obtained racemic hexestrol by the action of sodium on anethole hydrobromide, followed by demethylation. Guzman (152) claimed that he was able to improve the Docken–Spielman synthesis by passing gaseous hydrogen bromide into anethole for 4 hr. instead of 20 min. and by isolating and purifying the anethole hydrobromide. According to a Japanese patent (10) anethole hydrobromide can be converted into hexestrol dimethyl ether by using the magnesium–magnesium iodide complex; demethylation with hydrogen iodide in acetic acid at 140–150°C. was almost quantitative. Fu and Sah (411) improved the yield of hexestrol dimethyl ether in the Bernstein and Wallis synthesis from 8 to 20 per cent by condensing 3-bromo-3-(*p*-ethoxyphenyl)propane with copper bronze; aluminum iodide was found to be an excellent dealkylating agent. Torf and Khromov-Borisov (508) condensed α-chloropropylbenzene to a mixture of *meso*-3,4-diphenylhexane and racemic 3,4-diphenylhexane by magnesium and a little iodine in ether solution. Nitration of the meso form to 3,4-bis(*p*-nitrophenyl)hexane in 66 per cent yield, reduction to the diamine in 82.4 per cent yield, and conversion, via the diazo reaction, to the dihydroxy compound in 73.4 per cent yield gave hexestrol. Luis (268) obtained a 50–60 per cent yield of *p*-(α-chloropropyl)anisole by reacting anisole and propionaldehyde in acetic acid–hydrochloric acid. Treatment of the chloro compound with magnesium in ether was claimed to give an almost quantitative yield of hexestrol.

The Kharasch–Kleiman Grignard synthesis (236) was reinvestigated by Wilds and McCormack (554), using phenylmagnesium bromide and anethole hydrobromide in the presence of cobaltous chloride. Kharasch and Kleiman had claimed a 42 per cent yield of hexestrol dimethyl ether; Wilds and McCormack found that ethylmagnesium bromide gave 29–31 per cent yields of the ether and that all other Grignard reagents, including phenylmagnesium bromide, gave yields of only 23–25 per cent. With anethole hydrochloride much lower yields were obtained, and anethole hydroiodide proved useless. This work revealed that temperatures up to 30°C. had little effect on yields of the ether and that, contrary to the reports of Kharasch and Fields (235) and of Kharasch and Sayles (238), the higher temperatures gave the better yields. Ether was found to be essential as solvent, for in benzene alkylations occurred. The method of Docken and Spielman (96), which used magnesium as coupling agent, was improved by Wilds and McCormack by the addition of cobaltous chloride, indicating that the synthesis proceeds via a Grignard reagent. From the reaction using ethylmagnesium bromide and anethole hydrobromide Wilds and McCormack were able to isolate a 25–30 per cent yield of racemic hexestrol dimethyl ether in addition to the meso form. The mechanism proposed by Kharasch and Kleiman for the reaction was as shown below:

$$C_6H_5MgBr + CoCl_2 \rightarrow C_6H_5CoCl + MgBrCl$$

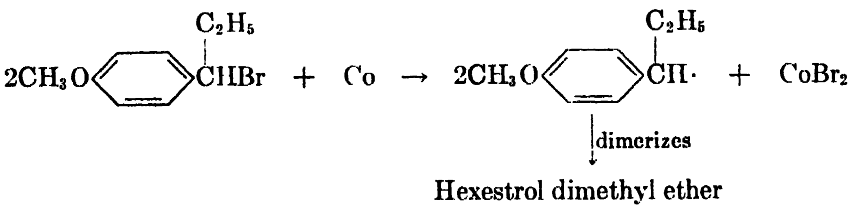
$$2C_6H_5CoCl \rightarrow C_6H_5C_6H_5 + 2\cdot CoCl$$



On the basis of their results Wilds and McCormack postulated a Wurtz-type coupling, the free radicals being produced by the action of metallic cobalt on the anethole hydrobromide.

$$2C_2H_5MgBr + CoCl_2 \rightarrow (C_2H_5)_2Co + MgBr_2 + MgCl_2$$

$$(C_2H_5)_2Co \rightarrow C_2H_4 + C_2H_6 + Co$$



Support for the mechanism was obtained by showing that finely divided cobalt could convert anethole hydrobromide to hexestrol dimethyl ether in 8.5 per cent yield.

From a study of the demethylation of hexestrol dimethyl ether, Kharag (232) concluded that the best method was to reflux the ether for 4 hr. with fifteen parts of hydriodic acid (density 1.65–1.70); he claimed an 86 per cent yield of hexestrol. Hughes and Thompson (198) demethylated hexestrol dimethyl ether by the novel method of heating for 4 hr. at 200°C. with thiophenol in alcoholic potassium hydroxide or merely in water. Group migration occurred with the formation of hexestrol quantitatively and of thioanisole. The method was also applied to diethylstilbestrol dimethyl ether (199). An interesting observation due to Wilds and McCormack (553) was that pyridine hydrochloride at 210°C. converted hexestrol monomethyl ether monobenzoate into the monobenzoate.

2. *Syntheses utilizing the addition of Grignard reagents to α,β-unsaturated systems*

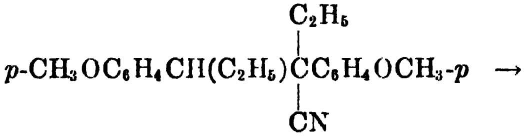
Developing this newer method, based on the previous work of Kohler (243), Wawzonek (538) added ethylmagnesium bromide across α-(*p*-methoxyphenyl)-*p*-methoxycinnamonitrile (XLIV).

$p\text{-}CH_3OC_6H_4CH{=}C(CN)C_6H_4OCH_3\text{-}p \rightarrow$

XLIV

$[p\text{-}CH_3OC_6H_4CH(C_2H_5)C(CN)C_6H_4OCH_3\text{-}p]^+MgBr^- \rightarrow$

XLV



$$p\text{-}CH_3OC_6H_4CH(C_2H_5)\underset{\displaystyle CN}{\overset{\displaystyle C_2H_5}{\overset{|}{\underset{|}{C}}}}C_6H_4OCH_3\text{-}p \rightarrow$$

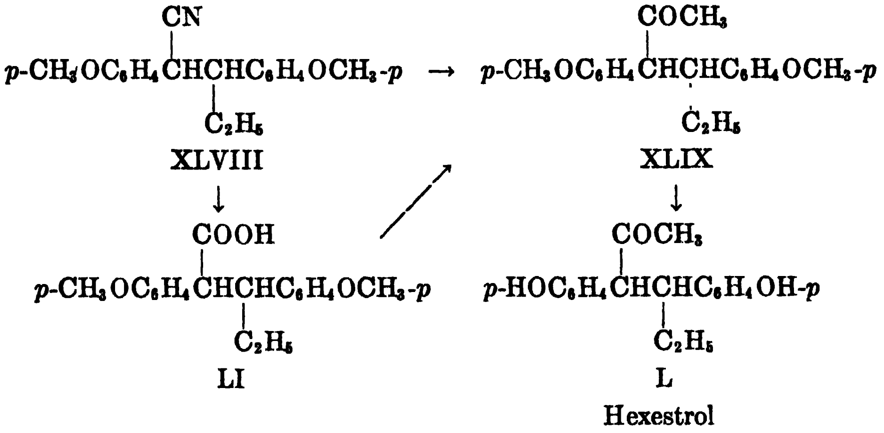
XLVI

$p\text{-}CH_3OC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4OCH_3\text{-}p$

XLVII

Direct treatment of the Grignard reaction product (XLV) with ethyl iodide yielded an oil from which crystalline α-ethyl-α,β-bis(*p*-methoxyphenyl)valeronitrile (XLVI), m.p. 73–74°C., was obtained. The mother liquors yielded a glassy isomer. Treatment of the oily nitrile mixture with sodium in isoamyl alcohol gave a mixture of hexestrol dimethyl ethers (XLVII) in 80 per cent yield, from which the meso ether was obtained in 33 per cent yield.

In related work Burckhalter and Sam (41) obtained XLIV in 95 per cent yield by condensing *p*-methoxybenzyl cyanide and anisaldehyde; this was a slight improvement over previous results (202, 311). Subsequent reaction of XLIV with an excess of ethylmagnesium bromide gave the diastereoisomeric forms of α,β-bis(*p*-methoxyphenyl)valeronitrile (XLVIII): one form, melting at 131°C., was obtained in 42 per cent yield; the other, an oil, in 49 per cent yield. The solid nitrile, treated with a 3 molar excess of methylmagnesium iodide in ether–benzene, gave an 87 per cent yield of 3,4-bis(*p*-methoxyphenyl)-2-hexanone (XLIX), m.p. 143°C., and a small amount of the diastereoisomer, m.p. 104°C. Rorig (366) had failed to achieve this conversion, owing to the use of an insufficient quantity of the Grignard reagent. In an alternative route to XLIX Burckhalter and Sam hydrolyzed the solid nitrile (XLVIII) to an acid (LI), m.p. 181–183°C. An isomeric lower-melting acid claimed by Hunter and Korman (202) was not found. The acid, as its acid chloride, reacted with ethoxymagnesiomalonic ester (532) to give, finally, the ketone XLIX. Conversion of



$$p\text{-}CH_3OC_6H_4\overset{CN}{\overset{|}{C}}H\underset{\underset{C_2H_5}{|}}{C}HC_6H_4OCH_3\text{-}p \rightarrow p\text{-}CH_3OC_6H_4\overset{COCH_3}{\overset{|}{C}}H\underset{\underset{C_2H_5}{|}}{C}HC_6H_4OCH_3\text{-}p$$

XLVIII → XLIX

$$p\text{-}CH_3OC_6H_4\overset{COOH}{\overset{|}{C}}H\underset{\underset{C_2H_5}{|}}{C}HC_6H_4OCH_3\text{-}p \qquad p\text{-}HOC_6H_4\overset{COCH_3}{\overset{|}{C}}H\underset{\underset{C_2H_5}{|}}{C}HC_6H_4OH\text{-}p$$

LI L

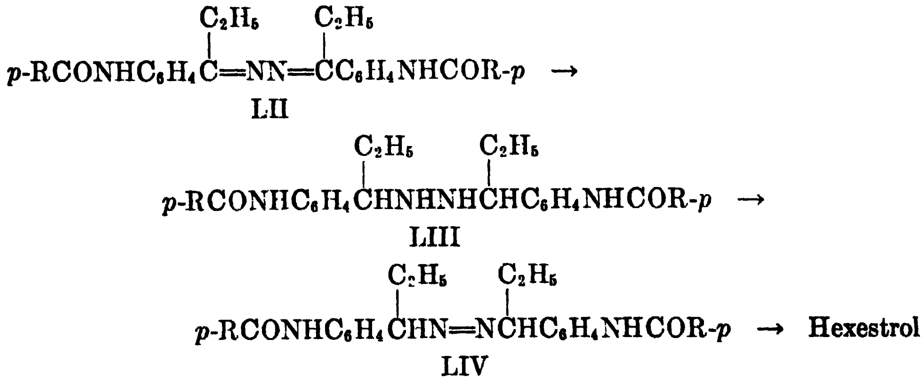
Hexestrol

XLIX to hexestrol was carried out by demethylation with aluminum bromide in benzene (the only satisfactory reagent), followed by Huang-Minlon reduction; an 81 per cent yield of hexestrol was obtained. Direct Huang-Minlon reduction of XLIX with long heating gave hexestrol in 48–52 per cent yield. Reaction of L with acetic anhydride gave a diacetate melting at 143–144°C. and the residues from the preparation of L gave an isomeric diacetate, m. p. 103–104°C.; each on hydrolysis regenerated the original ketone.

3. Syntheses involving azine intermediates

This type of synthesis was first used to obtain hexestrol by Campbell, Dodds, and Lawson (54); it is notorious for poor yields. Sah (375) used an essentially similar synthesis. Anisaldazine was treated with ethylmagnesium iodide and the product pyrolyzed at 300°C. in dibenzyl ether; demethylation with hydriodic acid gave hexestrol.

In a method (258) based on the original one of Bretschneider, Bretschneider, and Ajtai (35) an acylated *p*-aminopropiophenone was converted by hydrazine hydrate to the ketazine LII. Catalytic reduction of LII followed by air oxidation gave LIV via the intermediate LIII. Fusion of LIV gave a mixture of the meso and racemic forms of the diacyl derivative of 3,4-bis(*p*-aminophenyl)-



$$p\text{-}RCONHC_6H_4\overset{C_2H_5}{\overset{|}{C}}{=}NN{=}\overset{C_2H_5}{\overset{|}{C}}C_6H_4NHCOR\text{-}p \rightarrow$$

LII

$$p\text{-}RCONHC_6H_4\overset{C_2H_5}{\overset{|}{C}}HNHNH\overset{C_2H_5}{\overset{|}{C}}HC_6H_4NHCOR\text{-}p \rightarrow$$

LIII

$$p\text{-}RCONHC_6H_4\overset{C_2H_5}{\overset{|}{C}}HN{=}N\overset{C_2H_5}{\overset{|}{C}}HC_6H_4NHCOR\text{-}p \rightarrow \text{Hexestrol}$$

LIV

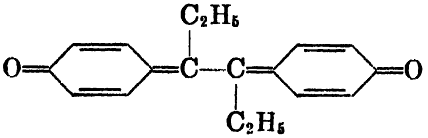
hexane. Hydrolysis of the separated diacyl derivatives followed by the diazo reaction, gave, with the meso diamine, hexestrol. Foldi and Fodor (132) and Fodor (130) applied the same method to *p*-methoxypropiophenone, and a patent (72) described the use of *p*-hydroxy-, *p*-alkoxy-, or *p*-acyloxypropiophenones as starting materials.

Fodor and Wein (131) investigated various applications of this synthesis as routes to 3,4-bis(*p*-aminophenyl)hexanes which may be converted to hexestrols as described. From *p*-acetamidopropiophenone a mixture of the meso and racemic diamino compounds was obtained; starting from *p*-aminopropiophenone only, the meso diamino compound was produced. The meso diamino compound was the final product also when the synthesis was applied to *p*-bromopropiophenone, followed by treatment of the dibromo compound obtained with cuprous iodide and aqueous ammonia at 205°C. in a sealed tube. A last route used propiophenone itself, which yielded meso and racemic 3,4-diphenylhexanes; separation of these, followed by nitration and catalytic reduction, gave the meso and racemic diamines. Application of the diazo reaction provided meso and racemic hexestrol.

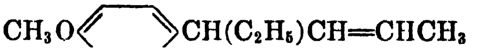
4. Other methods

Huang-Minlon (191) reacted *p*-nitropropylbenzene with hydrazine hydrate and potassium hydroxide in triethylene glycol and obtained a mixture of *p*-aminopropylbenzene and both forms of 3,4-bis(*p*-aminophenyl)hexane; the latter were converted to the hexestrols by the diazo reaction. In the absence of potassium hydroxide reduction but no coupling occurred. The compound 3,4-bis(*p*-methoxyphenyl)-3-hexanol, previously described in connection with the Dodds and related syntheses, was converted directly to hexestrol dimethyl ether by Sah (374) by subjecting it to Clemmensen reduction. Alternatively, Clemmensen reduction of 3,4-bis(*p*-methoxyphenyl)-3,4-hexanediol gave hexestrol dimethyl ether. Turnbull (510, 511) obtained 3,4-bis(*p*-methoxyphenyl)-3,4-dibromohexane by the addition of bromine to diethylstilbestrol dimethyl ether or by the irradiated bromination of hexestrol dimethyl ether in the presence of dibenzoyl peroxide. Treatment of the dibromo compound with potassium iodide in acetone or zinc dust in acetic acid gave hexestrol dimethyl ether, thus providing a method for the transformation of diethylstilbestrol into hexestrol.

Adler (1, 178) obtained α,α'-diethylstilbenequinone (LV) by the oxidation of diethylstilbestrol with lead dioxide, ferric chloride, silver oxide, or lead tetra-



LV



LVI

acetate. The compound was obtained pure, whereas previous preparations were brown-red resins (122). Hydrogenation of LV led largely to the *trans*-diethylstilbestrol. Both *cis*- and *trans*-stilbestrols may be oxidized to the quinone, and since hydrogenation gives the *trans*-stilbestrol the reactions provide a chemical method for cis-to-trans interconversion. Diethylstilbestrol was converted to 3,4-bis(*p*-hydroxyphenyl)-2,4-hexadiene in 73 per cent yield by rearrangement of the quinone with sodium hydroxide solution; acids also bring about this rearrangement. Subsequent hydrogenation of the diene with palladium–charcoal gave a 50 per cent yield of hexestrol, together with some racemate. Hydriodic acid and red phosphorus may also be used as the reducing agent. The diene referred to melted at 184–185°C. and was called isodienestrol, since it was different from the isomeric dienestrol of Dodds (101, 102), which melted at 227–228°C.

It may be noted that direct hydrogenation of diethylstilbestrol gives an almost quantitative yield of racemic hexestrol (391).

The pinacolone alcohol 3,3-bis(*p*-hydroxyphenyl)-4-hexanol, previously mentioned in connection with the synthesis of diethylstilbestrol, on retropinacolone rearrangement with hydrogen iodide was simultaneously reduced to give a 20 per cent yield of hexestrol (3, 175).

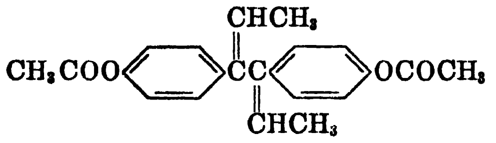
Reesor, Smith, and Wright (346) metalated stilbene with sodium and reacted the disodium derivative with an alkyl halide, thus obtaining a mixture of meso and racemic α,α'-dialkyldiphenylethanes.

Tanabe and Onishi (497) obtained hexestrol dimethyl ether by the condensation of LVI with anisole by the action of sulfuric acid at 10°C.

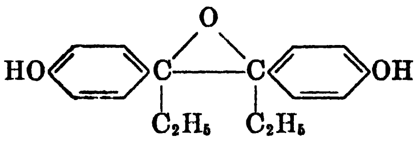
C. SYNTHESES OF DIENESTROL

1. *Syntheses via 3,4-bis(p-hydroxyphenyl)-3,4-hexanediol*

Dienestrol, the third principal stilbene-type estrogen, was first obtained by Dodds, Golberg, Lawson, and Robinson (101, 102) by acetyl chloride dehydration of 3,4-bis(*p*-hydroxyphenyl)-3,4-hexanediol (XXXVII). Although other methods have been used to synthesize dienestrol (447), this method has received most attention. The 3,4-bis(*p*-hydroxyphenyl)-3,4-hexanediol obtained by Dodds et al. was a mixture of diastereoisomers, and the mixture was separated into its meso and racemic forms by Adler and Lundin (6). These workers acetylated the mixture with acetic anhydride; on cooling the higher-melting meso diacetate (m.p. 208–210°C.) separated in 58.5 per cent yield. The racemic diacetate, m.p. 83–84°C., was obtained as the monoalcoholate by addition of water to the filtrate, extraction with ether, and recrystallization from ethanol. The diacetates were hydrolyzed to the corresponding pinacols, m.p. 217–219°C. and m.p. 212–214°C., and dehydrated by means of acetic anhydride–acetyl chloride. The meso compound gave the diacetate of 3,4-(*p*-hydroxyphenyl)-2,4-hexadiene or dienestrol diacetate (LVII) in 71 per cent yield; the racemic form also gave dienestrol diacetate but in 47 per cent yield. Both pinacols also gave the same rearrangement product, the pinacolone XXXVIII. A compound melting at 94–95°C. had been previously obtained by Hobday and Short (172) and had been thought to be a diastereoisomeric form of 3,4-bis(*p*-hydroxyphenyl)-3,4-hexanediol. Adler and Lundin considered that this compound might be 3,4-epoxy-3,4-bis(*p*-hydroxyphenyl)hexane (LVIII).



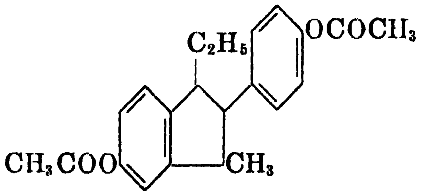
LVII



LVIII

The original Dodds synthesis gave only 25–30 per cent yields of dienestrol; the method of Adler and Lundin using isomer separation gave 64 per cent total yields of the estrogen. This superior method of synthesis of dienestrol is the basis of several patent claims (2, 176, 177). Other modifications, such as the use of sodium, potassium, or calcium amalgams to convert *p*-hydroxypropiophenone to the pinacol and the use of benzoyl chloride or *p*-toluenesulfonyl chloride as acylating agent, have been introduced (170, 171, 409).

Three dienestrols are now known. α-Dienestrol or dienestrol, m.p. 227–228°C., was obtained by Dodds, Golberg, Lawson, and Robinson (101, 102). β-Dienestrol or isodienestrol, m.p. 184–185°C., was prepared by Hobday and Short (172) and was also obtained, as previously mentioned, a year later by v. Euler and Adler (122). A third isomer, γ-dienestrol, m.p. 121–122°C., was obtained by Breivogel in 1948 (252). The isolation of the three dienestrols led Lane and Spialter (252) to investigate the nature and amounts of dienestrols and other products obtained in the dehydration of the meso and racemic pinacols. These authors also introduced the α-, β-, γ-dienestrol nomenclature. Dehydration of 3,4-bis(*p*-acetoxyphenyl)-3,4-hexanediol with acetic anhydride–acetyl chloride, followed by chromatography of the product on silicic acid, gave four fractions. One fraction contained the diacetates of the three dienestrols, together with that of indenestrol A (LIX). This latter compound had been obtained previously by the cyclization of dienestrol by Adler and Hagglund (4) and by Hausmann and Wilder Smith (158, 159). The dienestrols could not be separated, but the α- and γ-isomers were estimated by reaction of the mixture with bromine in acetic acid in the presence of sodium acetate. The α- and γ-diacetates react rapidly with the reagent, while the β-diacetate and that of indenestrol A do not; titration gave the combined α + γ content. A second fraction was 3,3-bis(*p*-acetoxyphenyl)-4-hexanone, the intermediate for the synthesis of diethylstilbestrol. A third fraction contained polymerized dienes, and some unreacted pinacol was also obtained as a separate fraction.



LIX

In later work Lane and Spialter (253) examined the dehydration and pinacolic rearrangement competition when the isomeric 3,4-bis(*p*-acetoxyphenyl)-3,4-

hexanediols were treated with acidic reagents and so clarified the conditions for obtaining diethylstilbestrol or dienestrol from this same starting material. The reagents acetyl chloride–acetic anhydride and hydrogen chloride–acetic anhydride gave dienestrols; the meso pinacol was more easily dehydrated than the racemic one. Apparently acetyl chloride is essential to the formation of dienestrol; the second reagent contains acetyl chloride produced by the interaction of hydrogen chloride and acetic anhydride (525). The function of acetic anhydride is apparently solely as a solvent; in pure acetyl chloride the dehydration was almost quantitative. When formic acid, sulfuric acid in acetic anhydride, or hydrogen chloride in acetic acid was used, the pinacolone was exclusively produced. The possible mechanisms for these changes were discussed by the authors. A preliminary acetylation step was suggested for the conversion of the pinacol to the diene.

2. *Other methods*

Turnbull (510, 511, 512) obtained 3,4-bis(*p*-acetoxyphenyl)-3,4-dibromohexane by the bromination of diethylstilbestrol and hexestrol diacetates under the conditions previously described. Treatment of this compound with potassium iodide in ethyl alcohol or with pyridine under nitrogen yielded dienestrol.

III. Some Physicochemical Considerations

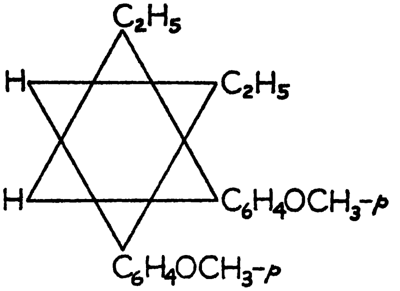
A. ISOMERISM

Theoretically two diethylstilbestrols must exist, a cis isomer and a trans isomer. The highly active diethylstilbestrol, m.p. 171°C., is considered from a variety of evidence (449) to be the trans isomer. A substance previously mentioned, melting at 141°C., was obtained by Dodds, Golberg, Lawson, and Robinson (100) and was later purified by Walton and Brownlee (533), who obtained from it both the trans isomer and a compound melting at 151°C.; the latter was called ψ-stilbestrol and was provisionally considered to be the cis isomer.

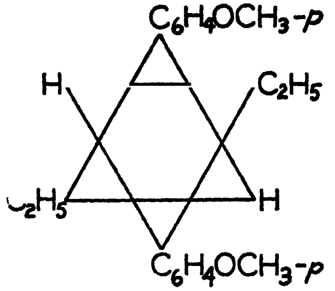
More recently, Wessely, Bauer, Chwala, Plaichinger, and Schönbeck (544) also failed to rearrange the trans isomer to the cis form. Treatment of *trans*-diethylstilbestrol with propionic anhydride in pyridine at 25°C. gave a 100 per cent yield of the known trans dipropionate, m.p. 105–106°C. The known cis dipropionate, m.p. 79°C., was obtained by ultraviolet irradiation of the trans dipropionate or in 30 per cent yield from *trans*-diethylstilbestrol and propionic anhydride at 50–100°C. Iodine in benzene did not isomerize the cis dipropionate. Hydrolysis of the cis dipropionate with methanolic sodium hydroxide gave only the *trans*-diethylstilbestrol. Hydrolysis with alcoholic ammonia at room temperature yielded some cis dihydroxy compound, but this could not be isolated in the pure state. Methylation of the cis dipropionate with methyl sulfate and 20 per cent sodium hydroxide solution gave the cis dimethyl ether. These workers also obtained the *cis*- and *trans*-2,3-bis(*p*-methoxyphenyl)-2-butenes, melting at 50°C. and 131°C., respectively. Similar and supporting results were obtained by Derkosch and Friedrich (89), who also failed to obtain pure *cis*-diethylstilbestrol by the hydrolysis of its dipropionate. By a spectroscopic method these workers found that hydrolysis of the cis dipropionate with alcoholic ammonia at 20°C. gave a stable solution of the cis dihydroxy compound, but a pure specimen of the latter could not be isolated. Use of alcoholic sulfuric acid at 20°C. as the hydrolyzing agent gave the *cis*-diethylstilbestrol, but this rapidly isomerized in solution to the trans isomer. Hydrolysis of the trans dipropionate with either reagent regenerated the trans dihydroxy compound.

These results clearly indicate that *cis*-diethylstilbestrol has not yet been obtained as a pure compound; indeed, it may be too labile for isolation. It is expected to have a melting point of about 110°C. In view of these facts Wessely and coworkers considered the substance melting at 151°C., *ψ*-stilbestrol, to be a geometric isomer of 3,4-bis(*p*-hydroxyphenyl)-2-hexene which they had obtained previously (345) with a melting point of 153°C.; the other isomer has a melting point of 143°C. The identity of the 3,4-bis(*p*-hydroxyphenyl)-2-hexene, m.p. 153°C., with *ψ*-stilbestrol had been previously suggested by Jones (217). Contrary to the earlier report of Walton and Brownlee, Malpress (276) found that heating the trans or *ψ* compound with 2.5 *N* aqueous hydrochloric acid produced an equilibrium mixture of the trans and *ψ* compounds in the ratio 9:1. This result is of importance in the chemical estimation or bioassay of the products of hydrolysis of the conjugated forms of diethylstilbestrol from biological fluids; hexestrol is quite stable under these hydrolyzing conditions. Buckles (39) made the interesting observation that ultraviolet irradiation of *cis*- or *trans*-stilbene in dilute alcoholic solution for 20 days yielded phenanthrene. Simamaru and Suzuki (414) found that *cis*- or *trans*-α,α'-dimethylstilbene with a little sulfuric acid at 210°C. gave an equilibrium mixture containing 55 per cent of the trans and 45 per cent of the cis isomer. Iodine at 210°C. gave *meso*-2,3-diphenylbutane; bromine produced some isomerization and also gave some 1,4-dibromo-2,3-diphenyl-2-butene.

The hexestrols exist as the meso isomer, m.p. 185°C., the racemic isomer, m.p. 129°C., and the antipodes, m.p. 80°C., of the latter (452). The meso isomer is the potent estrogen; the racemic form is frequently referred to as isohexestrol. The evidence for the assignment of configuration was obtained earlier (452). Using hexestrol dimethyl ether as model, Suetaka (476) considered the possibility of rotational isomerism about the central carbon–carbon bond in *meso*-hexestrol. Assuming the possibility of gauche (LX) and trans (LXI) forms, Suetaka calculated their dipole moments as 2.06 D and 1.75 D, respectively. The observed moment in carbon tetrachloride solution was 1.77 D, showing that the trans form is almost the sole species present. This result is expected on steric grounds, but the observed dipole moment of 1.57 D in benzene is difficult to interpret. The confirmation of the trans form for *meso*-hexestrol in solution is important, in that under physiological conditions *meso*-hexestrol will exert its biological action in a structural form corresponding to that of the natural estrogens. Suetaka also found a dipole moment in benzene solution of 1.24 D for *trans*-α,α'-bis(methylthio)stilbene (LXII). Assuming no anomalies, this value was shown to be compatible with a structure in which the aromatic rings are rotated 75° from the plane of the ethylenic unit and the methyl groups rotated 34° from this plane in the opposite directions and about the sulfur-carbon bonds. These steric effects of the aliphatic portion seem of considerable importance in estrogen chemistry and are discussed later.



LX



LXI

$C_6H_5C(SCH_3){=}C(SCH_3)C_6H_5$

LXII

α-Dienestrol or dienestrol, m.p. 227–228°C., the potent estrogen, was considered to have the trans-trans structure (57). As will be discussed later, this configuration for dienestrol has been substantiated. On the basis of estrogenic activities the γ-isomer, m.p. 121–122°C., is probably the cis-trans form, while the β-isomer, m.p. 184–185°C., also called isodienestrol, is probably the cis-cis form.

B. SPECTROSCOPIC STUDIES

Early work by Ley and Rincke (261) and by Arends (11) showed that the ultraviolet absorption spectrum of *trans*-stilbene has its maximum shifted to progressively shorter wavelengths by the introduction of one, and then two, methyl substituents on the alkene unit. This maximum is attributed to the triple chromophore consequent from the electron interaction in the two aromatic rings with the ethylenic system. It is of interest that the saturated carbon system in bibenzyl also is chromolatory (32). Oki (320) gave the ultraviolet absorption data in table 1 for various 4,4′-dimethoxy-α,α′-dialkylstilbenes.

There is a shift of the maximum further to shorter wavelengths with increasing size of the alkyl group, and the steric effect of an α-alkyl group on the ortho hydrogen of the α′-phenyl group was proposed by Jones (218) and Lewis and Calvin (260) as an explanation of the spectroscopic effect.

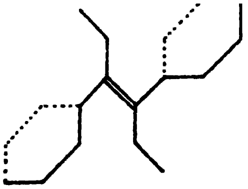
Jeffrey, Koch, and Nyburg (214) and Koch (239) concluded from a study of molecular models, x-ray crystallographic data, and ultraviolet absorption data that in α,α′-dialkylstilbenes, and hence diethylstilbestrol, the desire to attain coplanarity and the full resonance energy of the *trans*-stilbene stystem is prevented by the steric effect of the alkyl groups. These molecules will therefore have their aromatic rings rotated, and it was presumed symmetrically, so that a staggered configuration (LXIII) is acquired. This structural characteristic is

TABLE 1

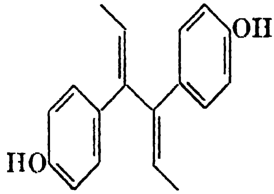
Ultraviolet absorption data for some 4,4'-dimethoxy-α,α'-dialkylstilbenes in 95 per cent ethanol

$p\text{-}CH_3OC_6H_4C(R){=}C(R)C_6H_4OCH_3\text{-}p$

R in compound	λ_{max}	$\epsilon_{max} \times 10^{-4}$	R in Compound		$\epsilon_{max} \times 10^{-4}$
	mμ			mμ	
H. . ..	230	1.27	CH_3 ..	247	2.85
	305	3.47	C_2H_5.	236	2.20
	326	3.37	C_3H_7	235	1.81



LXIII



LXIV

present in bibenzyl (358). The ethyl groups in diethylstilbestrol were considered oriented away from the phenyl groups for steric reasons. This conclusion refuted the idea that diethylstilbestrol simulated the natural estrogens but only on the point of the orientation of the ethyl groups. The fact that diethylstilbestrol is the trans isomer and, from the work of Jeffrey, Koch, and Nyburg, has definite thickness, make the similarity to the natural estrogens closer than was originally appreciated. The staggered configuration also applies to hexestrol, but here it is an intrinsic rather than an enforced characteristic. Similar conclusions were drawn about dienestrol (214); in this compound the data indicated a rotation of 50° for the phenyl groups from the plane of the hexadiene system, the latter having the trans-trans form (LXIV). This configuration would be expected in view of the relation to diethylstilbestrol and its estrogenic potency. It is expected that the cis phenyl group in triphenylethylene will have a steric effect, particularly on its adjacent phenyl group. Braude (32) found that isodienestrol showed styrene chromophore adsorption corresponding to the summation of two 4-hydroxy-β-methylstyrene systems. This was considered to indicate that the two halves of the isodienestrol molecule were rotated about the central carbon–carbon bond into planes approximately at right angles. This configuration would be expected for the cis-cis structure and, as pointed out previously, this is also in agreement with the biological results. While Jeffrey, Koch, and Nyburg considered rotation of the aromatic rings in these compounds into parallel planes, Oki (320) considered the direction of rotation to be ambiguous. However, consideration of the biological results for dienestrol and isodienestrol indicates that rotations which tend to bring the nuclei into planes at right angles will lead to decreased estrogenic activity; active estrogens are expected to have the staggered configuration. Havinga and Nivard (160) also concluded from spectroscopic data that diethylstilbestrol has a nonplanar structure and suggested that in *cis*-cinnamic acid nonplanarity of the carboxyl group and the aromatic ring is important for the activity of the compound as a plant hormone.

Oki and Urushibara (327) concluded from spectroscopic data that thickness of the molecule of diethylstilbestrol is important for its estrogenic activity and that this compound had optimum thickness. These authors pointed out that thickness and width were complementary and that the width may also be important for biological activity. However, thickness is the factor responsible for orienting the phenolic groups, and from the existence of estrogenic activity in many large molecules, width appears to be a very secondary factor. In support of the hypothesis of molecular thickness, these authors showed 4,4′-dimethoxy-α,α'-bis(methylthio)stilbene, which is active at 10 micrograms in mice, to have a molecular thickness similar to that of the corresponding α,α'-dipropylstilbene. It appears that ethyl groups are not fundamental to activity and that other sterically similar groups can replace them. Pursuing these ideas Oki (321) correlated estrogenic activity and spectroscopic properties or molecular thickness in a series of 4,4′-dimethylthio-α,α'-dialkylstilbenes (table 2) and found optimum activity at optimum thickness corresponding to the diethyl compound.

Oki (320) replaced the alkyl groups by halogen atoms and prepared a series of 4,4′-dimethoxy-α,α'-dihalogenostilbenes; spectroscopically steric effects were found to be operative. The bromine atom, which has a van der Waals radius similar to that of the methyl group, was found to have a smaller steric effect on rotation of the ring. The dichloro compound (table 3) was found to have an estrogenic activity similar to that of the dibromo compound; whereas the latter molecule has a thickness of the same order as diethylstilbestrol, the chloro compound has not. This was interpreted as being due to the existence of another optimum molecular thickness to which the dichloro compound approximated. However this seems unlikely, and probably properties of these compounds other than molecular thickness are important. The reality of hindered rotation, and so molecular thickness, in these molecules was shown by Oki (321a). Resolution provided the first example of an optically active stilbene containing no asymmetric carbon atom.

The concept of optimum molecular thickness is probably of considerable im-

TABLE 2

Ultraviolet absorption data (in 95 per cent ethanol) and estrogenic activities for some 4,4′-bis(methylthio)-α,α'-dialkylstilbenes

$p\text{-}CH_3SC_6H_4CR{=}CRC_6H_4SCH_3\text{-}p$

R in Compound	λ_{max}	$\epsilon_{max} \times 10^{-4}$	Estrogenic Activity in Mice, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose‡
	mμ		*micrograms*
CH_3	271	3.1	300 (50%)
C_2H_5	266.5	2.7	40
C_3H_7	265	2.5	200 (incomplete)

‡ Compound administered in two portions.

TABLE 3

Ultraviolet absorption data (in 95 per cent ethanol) and estrogenic activities for some 4,4′ dimethoxy-α,α′-dihalogenostilbenes

$p\text{-}CH_3OC_6H_4CX{=}CX'C_6H_4OCH_3\text{-}p$

Compound			$\epsilon_{max} \times 10^{-4}$	Estrogenic Activity in Mice, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose‡
X	X′			
		mμ		*micrograms*
Cl	Cl	282	2.87	200
Br	Br	263	2.53	300
I	I	235	2.24	800 (inactive)
Cl	I	227	1.22	100
		267	1.27	
Br	I	234	1.72	> 600
		261	1.58	

‡ Compound administered in two portions.

portance in determining estrogenic activity and goes a long way towards explaining the low activity of compounds such as 4,4′-dihydroxystilbene and the varying activities of the alkylstilbestrols (450). Nevertheless it is clear from the above discussion that the nature of the steric factor and its effect on the molecule as a whole must also be considered.

C. ADSORPTION PROPERTIES

Rideal and Schulman (355) and Rideal (354) measured the adsorption capacity, on a gliadin monolayer, of various stilbene estrogens. The order of increasing adsorption capacity of these α,α′-dialkylstilbestrols was found to correspond essentially with the order of increasing estrogenic activities of the compounds. The peak of both properties was shown to occur with diethylstilbestrol. Variation of the aliphatic portion of diethylstilbestrol affects the estrogenic activity (450), and this variation was found by Rideal and Schulman to have a definite effect on the adsorption capacity of the substance. Adsorption at a chemoreceptor is probably an important requirement for an estrogen, and the results of Rideal and Schulman indicate that the aliphatic portion may make an important contribution to such van der Waals adsorption. This is probably an important second function of the aliphatic portion and would account for the need for a steric factor having suitable adsorption capacity.

D. SOLUBILITY

Cheymol and Carayon-Gentil (57, 67) determined the solubilities of diethylstilbestrol, hexestrol, and dienestrol in various solvents (table 4).

Unfortunately, few data in this direction are available, although solubilities are probably of considerable significance to estrogenic potency. Water solubility confers high translocatability, and in general water-soluble estrogens have a more rapid action. Effort has been expended to produce water-soluble estrogens, since these may be administered intravenously.

An interesting observation due to Wilder Smith and Williams (420) was the

TABLE 4

Some solubility data for diethylstilbestrol, hexestrol, and dienestrol

Solvent	Solubility		
	Diethylstilbestrol 15–18°C.	Hexestrol 15–18°C.	Dienestrol 15–18°C.
	g /100 cc.	*g./100 cc.*	*g./100 cc.*
Water	0.028	0.007	0.0035
Ethyl alcohol (99%)	18.5	18.3	11.25
Methyl alcohol	7.5	24.55	13.6
Benzene	0.22	0.17	0.069
Chloroform	0.80	0.19	0.14
Ether	32.0	29.1	8.06
Ethyl acetate	23.51	33.0	18.55
Acetone	18.4	10.22	11.64
Dioxane	10 71	8.28	

instability of diethylstilbestrol and dienestrol in aqueous solution, particularly in acid or alkaline solution. Polymerization was suggested as a mechanism, since in neutral solution the loss of activity was greatly enhanced by traces of hydrogen peroxide but inhibited by hydroquinone. The instability of these substances in solution was also found, by chemical estimation, by Warren and Goulden (536). These results are of consequence in assaying these estrogens in solutions. Hexestrol and natural estrogens were found to be stable.

E. SOME STRUCTURAL CONSIDERATIONS IN RELATION TO ESTROGENIC ACTIVITY

Giacomello and Bianchi (139) found, by x-ray crystallography, that the molecules of diethylstilbestrol and of estrone were 8.55 A. long and 3.88 A. wide. Carlisle and Crowfoot (58) similarly found the trans configuration for solid *meso*-hexestrol, which thus simulates the natural hormones. In view of these results Ungnade and Morriss (517) examined the melting-point behavior of various estrogens. Diethylstilbestrol or hexestrol was found to form mixed crystals with "α"-estradiol; hence the compounds are isomorphic. Mixed-crystal formation with diethylstilbestrol and hexestrol was found and is evidence for the trans configuration of the former compound, since *cis*-stilbene does not form mixed crystals with the corresponding dihydro compound (304).

Schueler (388) used the results of Giacomello and Bianchi and concluded that a substance may be estrogenic if it consists of a rather large, rigid, inert molecule with two active hydrogen-bonding groups at an optimum separation of 8.55 A. The latter point was stressed, but the other suggestions were not elaborated. Estrone, which does not have two hydrogen-bonding groups, was considered to function as the enol or to be reduced *in vivo*. There is evidence in support of this latter idea (348, 349, 468). Devis (90), however, found 6-ketotestosterone acetate to have moderate estrogenic activity and attributed this to enolization of the carbonyl group. Macovski and Georgescu (272) suggested an optimum separation of oxygen atoms of 9.6 A. The suggestion of an optimum separation of hydrogen-bonding groups is of course quite incomplete without consideration of other factors. In any case, 8.55 A. is a molecular length, as shown for estrone

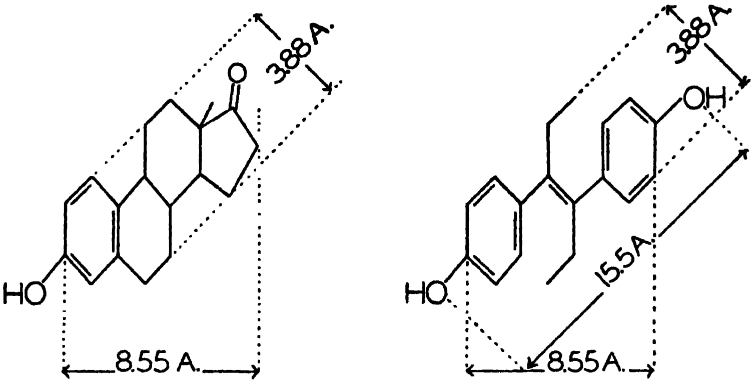
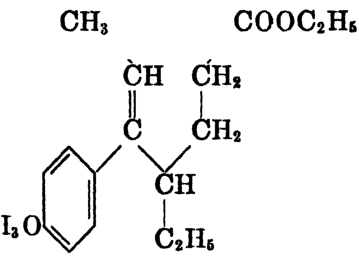


FIG. 1

and diethylstilbestrol (figure 1), and is not the distance of separation of hydrogen-bonding groups. For diethylstilbestrol this latter separation is about 15.5 A. Keasling and Schueler (228) modified the earlier suggestion and found, for 4,4′-substituted azomethines, an optimum separation of groups at 14.5 A. Schueler suggested that weaker hydrogen bonding groups and a separation of 9–10 A. was associated with androgenic activity. Velasquez, Valenzuela, and Aguilar (530) found the hydroxyl groups of diethylstilbestrol essential to its bacteriostatic activity. In agreement with the concept of hydrogen bonding the value of groups to an estrogenic molecule appears to be in the order alcoholic hydroxyl group < phenolic hydroxyl group < carboxyl group. As mentioned previously, Oki and his collaborators (323) considered that besides optimum separation of hydrogen-bonding groups appropriate orientation of the groups is necessary. This is attained by the molecule having thickness, although the staggered structure is probably of other stereochemical importance as well. Although the general shape of the aliphatic portion of the potent artificial estrogens does not resemble that in natural estrogens, it points to the presence of a possibly valuable stereochemical feature not possessed by natural estrogens.

Clark (73) found LXV to be estrogenically active and considered that the lack of van der Waals adsorption of the molecule at the chemoreceptor was made good by the potential carboxyl group, which might function as an anchoring group at a center on the chemoreceptor. Grundland (149, 150) suggested that,



LXV

in the body, estrogens and lipides form van der Waals adhesion complexes, the latter thereby temporarily acquiring polar groups and being more readily dispersed in the aqueous phase of the blood. This suggestion does not account for the influence of the number and spacing of hydroxyl groups on the estrogenic activity shown by a molecule. McShan and Meyer (280) found that diethylstilbestrol, hexestrol, and dienestrol inhibited the succinic oxidase system and that this was a function of the number of hydroxyl groups present. Vargas and Escubos (527) considered that estrogenic activity in a substance was related to its cellular permeability and that this was optimum in the more homopolar or trans forms of molecules.

IV. Estrogenic Activities of Diethylstilbestrol, Hexestrol, and Dienestrol

Owing to the operation of various factors, data for the estrogenic activities of substances have no absolute significance, as previously pointed out. Data from various sources for the three principal stilbene estrogens are collected in table 5. The data give some indication of the potencies of these compounds and are also useful as a guide.

Bishop, Kennedy, and Wynn-Williams (20) and Bishop, Richards, Neal-Smith, and Perry (21) attempted the assessment of estrogens in the human. The estrogen was administered orally and daily for 14 days to amenorrheic women, and the criterion of uterine bleeding upon the withdrawal of the estrogen was used. Dienestrol was found to have 25 per cent of the activity of diethylstilbestrol, while hexestrol had only 6 per cent of its activity. Doisynolic acid had 20 per cent of the activity of diethylstilbestrol, but ethinylestradiol was 20–25 times as potent. These authors found diethylstilbestrol to be more toxic at therapeutic dosage than the other estrogens and in higher dosage more likely to cause nausea. It appears that toxicity is related to estrogenic potency, since ethinylestradiol

TABLE 5

Estrogenic activities of diethylstilbestrol, the hexestrols, and the dienestrols

Compound	Melting Point	Estrogenic Activity inRats (100% Response Unless Indicated Otherwise); Minimal Effective Dose		Reference
		Subcutaneously	Orally	
	°C.	*micrograms*	*micrograms*	
Diethylstilbestrol	171	0.4		(102)
			5	(102)
Hexestrol (meso form)	186	0.2		(53)
			3	(102)
Hexestrol (racemic form)	129	1000		(54)
Hexestrol (+ antipode)	80	100		(549)
Hexestrol (− antipode)	80	1000 (40%)		(549)
α-Dienestrol	227-228	0.5		(102)
			3	(102)
β-Dienestrol	184–185	0.003 (α-isomer = 1)		(252)
γ-Dienestrol	121–122	0.03 (α-isomer = 1)		(252)

at higher dosage was toxic. Using rhesus monkeys and the criterion of uterine bleeding, Eckstein, Krohn, Zuckerman, and Healy (111) found the order of activity to be diethylstilbestrol > hexestrol > dienestrol; the estrogen was given as a single dose intramuscularly. The confusing and contradictory biological results (55, 112, 229) for the stilbene estrogens prompted Harmer and Broom (156) to attempt the correlation of the results on animals and the clinical results of Bishop and coworkers. In the rat hexestrol given orally in oil had 10 per cent of the activity of diethylstilbestrol, while dienestrol had 67 per cent of this activity. In aqueous solution and subcutaneously these orders were reversed; hexestrol had 67 per cent and dienestrol < 33 per cent of the activity of diethylstilbestrol. Ryden (371), using the criterion of proliferation in women, found that the activities were diethylstilbestrol > dienestrol > hexestrol. Ryden (372) also found, in women, that dienestrol was 5–6 times more active intramuscularly than orally, and that diethylstilbestrol was 1.5–2 times more active than dienestrol orally and 3–5 times more active than hexestrol. These results make interesting comparison with those in table 5 and clearly show the difficulties of comparing the estrogenic potencies of compounds. Munro and Kosin (298) found, on the basis of the response of the chick oviduct, that hexestrol was more active than diethylstilbestrol. Similarly, Dorfman and Dorfman (108) found 7-methylbisdehydrodoisynolic acid quite close in activity to diethylstilbestrol. In women and using gonadotropin excretion as the method of assay, Tokuyama, Leach, Sheinfeld, and Maddock (507) found diethylstilbestrol to be 5 times more active than "α"-estradiol. The oral efficiency of an estrogen is considered to be related to the ability of the liver to inactivate it. Nielsen, Pedersen-Bjergaard, and Tønnesen (314) found that diethylstilbestrol and dienestrol were not inactivated by the liver in the rat when given orally. Hexestrol, estrone, and "α"-estradiol did suffer inactivation; parenterally none of these estrogens was inactivated. Dienestrol has been reported to be 3 times more active subcutaneously than orally (256).

V. ESTERS AND ETHERS OF DIETHYLSTILBESTROL, HEXESTROL, AND DIENESTROL

A. ESTERS

Estrogens take several days to act and a readily absorbed compound is more readily eliminated. Such compounds will have short duration of activity and may even be inactive. Diethylstilbestrol and hexestrol, both orally and subcutaneously and in large or small dosage, are short acting (504). These difficulties have been overcome by injection in divided dosage or some other suitable mode of administration (98) or by the use of esters. The latter apparently require hydrolysis *in vivo* before exerting their estrogenic function and have protracted action (220). The hydrolysis of diethylstilbestrol dipropionate is most effective in the liver and the kidney (91). Emmens (113) considered the function of hydroxyl groups in diethylstilbestrol to be for elimination of the estrogen via esterification. This is hardly likely to be the primary purpose of the hydroxyl function. Zima, Ritsert, and Kreitmair (561) found that the duration of estrus in the rat provoked by a series of esters of diethylstilbestrol paralleled their ease of hydrolysis in alcoholic potassium hydroxide. This supports the concept of *in vivo* hydrolysis of esters and the need for free hydrogen-bonding groups. The long-acting esters have obvious clinical value.

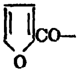
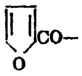
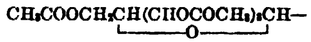
Esters have been prepared by the interaction of an organic acid chloride or anhydride or an inorganic acid chloride with the phenolic estrogen, in the presence or absence of an organic or inorganic base. Dienestrol esters were prepared (267) by reaction of the phenol with a Grignard reagent and subsequent treatment with an acylating agent. The minimal effective dose for an estrogen ester is higher than that of the parent estrogen; the effective dosage varies with the ester. Dienestrol difuroate has greater activity than the dibenzoate (75). Diethylstilbestrol and its dipropionate were fifteen times as effective as estrone in stimulating uterine growth (195). In rats diethylstilbestrol was found to be 8 times, and its dipropionate 2 times, as active as "α"-estradiol benzoate (195). Contrary to these results Veziris and Melzer (531) found "α"-estradiol benzoate more active than the dipropionates of hexestrol and diethylstilbestrol. Hexestrol dipropionate was more active than diethylstilbestrol itself (531). By the use of uterine bleeding upon withdrawal of the estrogen as a criterion and a single intramuscular dose in the rhesus monkey, "α"-estradiol and diethylstilbestrol dipropionates were found to be more active than the parent substances (111). Trimborn, Werle, and Semm (509) found the threshold dosage of dienestrol diacetate to be 0.25 microgram for mice intramuscularly, while for full estrus response 0.5 microgram was needed; twice these levels were required when the substances were administered orally.

Esterification is a chemical method for prolonging estrus; physical methods also have some importance. Increased duration was obtained by using an oily suspension of the estrogen; the duration of its action was found to depend on the particle size (124). Compressed implanted pellets still further extend the duration (286). However, other experiments indicated that prolongation with crystal suspensions occurred only at higher dosage (282, 537). A second type of ester based on an inorganic acid, generally sulfuric or phosphoric acid, is of importance, since the solubility of these esters or of their salts permits intravenous use and they have rapid action. The disulfate of diethylstilbestrol has a high activity in the rat, the guinea pig, and the rabbit and is tolerated at 10 mg., 20 mg. and 60 mg., respectively (146). Cavallini (60) found, in the guinea pig, that the disodium salt of diethylstilbestrol disulfate had about the same activity as diethylstilbestrol dipropionate, although it acted more rapidly. Harmer and Broom (156) found that an aqueous solution of potassium hexestrol sulfate given orally to the rat had only 7 per cent of the activity of a solution of diethylstilbestrol in oil. Given subcutaneously the salt solution had only 1 per cent of the activity of an aqueous solution of diethylstilbestrol. The alkali metal salts of diethylstilbestrol bis(sulfoacetate) (180) were claimed to show the full activity of the parent estrogen, besides having water solubility and low toxicity. A product melting at 164°C., containing four molecules of diethylstilbestrol to one of camphor, and prepared by intimate mixing or co-crystallization of the components was claimed to have therapeutic value (278). The esters of diethylstilbestrol, hexestrol, and dienestrol which have been prepared more recently are collected in tables 6, 7, and 8. Most of these have been prepared previously, but improved methods of

TABLE 6

Esters of diethylstilbestrol

$p\text{-}ROC_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_4OR'\text{-}p$

Compound		Melting Point	References
R	R'		
		°C.	
$CH_3CO—$	$CH_3CO—$	123	(351, 561)
			(401)
$CH_3CH_2CO—$	H—	92–94	(422)
$CH_3CH_2CO—$	$CH_3CH_2CO—$	107	(561)
		106–107	(423)
		105–106	(71)
		71–72 (isomeric form)	(71)
		104–106	(351)
$CH_3(CH_2)_2CO—$	$CH_3(CH_2)_2CO—$	98–99	(424)
		91	(561)
$CH_3CH_2OCH_2CO—$	$CH_3CH_2OCH_2CO—$	136.5–137.5	(289)
$CH_3CH_2SCH_2CO—$	$CH_3CH_2SCH_2CO$	95–97	(290)
		99–101	(289)
$CH_3CH_2OCO—$	$CH_3CH_2OCO—$	118	(425)
$CH_3(CH_2)_3CO—$	$CH_3(CH_2)_3CO—$	76.5–77.5	(426)
$CH_3CH_2CO—$	$CH_3(CH_2)_4CO—$		(427)
$CH_3(CH_2)_4CO—$	$CH_3(CH_2)_4CO—$	76	(561)
		75–76	(428)
$CH_3(CH_2)_5CO—$	$CH_3(CH_2)_5CO—$	58	(561)
$CH_3(CH_2)_6CO—$	$CH_3(CH_2)_6CO—$	60	(561)
		59–60	(429)
$CH_3(CH_2)_7CO—$	$CH_3(CH_2)_7CO—$	50	(561)
$CH_3(CH_2)_8CO—$	$CH_3(CH_2)_8CO—$	68	(561)
$CH_3(CH_2)_{10}CO—$	$CH_3(CH_2)_{10}CO—$	80	(561)
$CH_3(CH_2)_{12}CO—$	$CH_3(CH_2)_{12}CO—$	82–84	(430)
		82	(561)
$CH_3(CH_2)_{16}CO—$	$CH_3(CH_2)_{16}CO—$	84–86	(437)
$C_6H_5CO—$	H—		(431)
$C_6H_5CO—$	$C_6H_5CO—$	215	(561)
$C_6H_5SO_2—$	$C_6H_5SO_2—$	139	(561)
			(124)
$NaSO_3CH_2CO—$	$NaSO_3CH_2CO—$	228–230 (d.)	(180)
			(179, 181, 520)
$C_5H_5\overset{+}{N}H\overset{-}{S}O_3CH_2CO—$	$C_5H_5\overset{+}{N}H\overset{-}{S}O_3CH_2CO—$	223–225 (d.)	(520)
$HSO_3—$	$HSO_3—$		(146)
$NaSO_3—$	$NaSO_3—$		(60, 61, 410)
$KSO_3—$	$KSO_3—$		(410)
$\overset{-}{Cl}\overset{+}{N}H_3CH_2CO—$	$\overset{-}{Cl}\overset{+}{N}H_3CH_2CO—$	214 (d.)	(154)
$CH_3CH_2CO—$	 $CH_3COOCH_2CH(CHOCOCH_3)_2CH—$		(432)

preparation have been claimed. Few records of estrogenic activities have been made recently, but these have been given by Solmssen (453, 454).

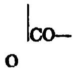
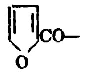
B. ETHERS

Ethers of diethylstilbestrol, hexestrol, and dienestrol have, in general, a more protracted estrogenic action than esters. This is presumably due to the greater

TABLE 7

Esters of hexestrol

$p\text{-}ROC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4OR'\text{-}p$

Compound		Melting Point	References
R	R′		
		°C.	
$CH_3CO—$	$CH_3CO—$	136–137	(287, 434) (69, 401)
$CH_3CH_2CO—$	$CH_3CH_2CO—$	123–124 119–120	(287) (69)
$CH_3CH_2CO—$	$CH_3(CH_2)_2CO—$		(287)
$CH_3CH_2OCO—$	$CH_3CH_2OCO—$	153–154	(436)
$CH_3(CH_2)_4CO—$	$CH_3(CH_2)_4CO—$	96–97	(287)
$CH_3(CH_2)_{16}CO—$	$CH_3(CH_2)_{16}CO—$	63	(69)
		177–178	(75)
$C_6H_5CO—$	$C_6H_5CO—$	235–237	(287) (69)
$HSO_3—$	$HSO_3—$		(444)
$NaSO_3—$	$NaSO_3—$		(60, 61, 410)
$KSO_3—$	$KSO_3—$		(410)
$H_2PO_3—$	$H_2PO_3—$		(13, 287)
$Na_2PO_3—$	$Na_2PO_3—$		(439)
$C_6H_5CO—$	$HOCH_2\underbrace{CH(CHOH)_3CH}_{O}—$	203–204	(433)
$C_6H_5CO—$	$CH_3COOCH_2\underbrace{CH(CHOCOCH_3)_3CH}_{O}—$	156	(433)

difficulty of fission of the ether link *in vivo*. It is a fact that ethers can be dealkylated *in vivo* (33, 470). Chedid and Horeau (66) found that methylation of the hydroxyl groups of "α"-estradiol and dimethylethylallenolic acid retarded their estrogenic activity by 6 hr. but did not diminish the intensity of their action. This is support for the need of free hydroxyl groups. Estrogens with free or esterified hydroxyl groups were found to be more effective against prostatic cancer than the corresponding ethers (479). Japp (213), using chicks and turkeys, found that diethylstilbestrol dimethyl ether was more potent than hexestrol dimethyl ether, diethylstilbestrol diethylstilbestrol dipropionate, diethylstilbestrol diethyl ether, or hexestrol. Hexestrol dimethyl ether was active in chicks but inactive in turkeys. These confusing results are obviously related to the metabolic processes of the test animals. Diethylstilbestrol is well known to have toxic effects, but it is not feasible to control them using the substance itself. Reid (347) prepared a series of diethylstilbestrol monoalkyl ethers and found that the monomethyl, mono-*n*-amyl, and mono-*n*-heptyl ethers were active in the rat at 3, 35, and 60 micrograms; thus they exhibit the general property of esters and ethers of decreased activity with increasing chain length of the acyl or alkyl group. It was claimed that these compounds are nontoxic and that the duration of their action can readily be controlled by the dosage. Hexestrol monoethers behave similarly (382). Cavallini, Goisis, and Massarani (64) found the bis(diethyl-

TABLE 8

Esters of dienestrol

$p\text{-}ROC_6H_4C(=CHCH_3)C(=CHCH_3)C_6H_4OR'\text{-}p$

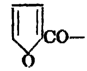
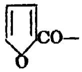
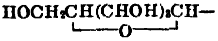
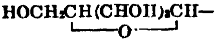
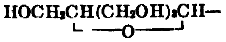
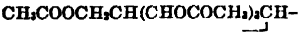
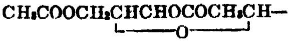
Compound		Melting Point	References
R	R'		
		°C.	
$CH_3CO—$	$CH_3CO—$		(267)
$CH_3CH_2CO—$	$CH_3CH_2CO—$		(267, 287, 438, 440)
$CH_3CH_2CO—$	$CH_3(CH_2)_2CO—$		(438)
$CH_3(CH_2)_2CO—$	$CH_3(CH_2)_2CO—$		(441)
$(CH_3)_2CHCH_2CO—$	$(CH_3)_2CHCH_2CO—$		(267)
		181–182	(75)
$C_6H_5CO—$	$C_6H_5CO—$	217–218	(75)
$NaSO_3—$	$NaSO_3—$		(410)
$KSO_3—$	$KSO_3—$		(410)

TABLE 9

Ethers of diethylstilbestrol

$p\text{-}ROC_6H_4C(C_2H_5)=C(C_2H_5)C_6H_4OR'\text{-}p$

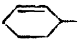
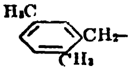
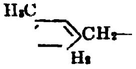
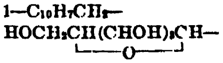
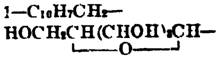
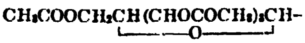
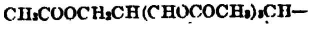
Compound		Melting Point	References
R	R'		
		°C.	
$CH_3—$	$H—$	110	(347)
			(138, 300, 380)
CH_3-	CH	121.5–123	(322)
		123	(347)
			(138, 300, 386)
$NaOOCCH_2—$	$NaOOCCH_2—$		(103)
$CH_2=CHCH_2—$	$CH_2=CHCH_2—$	93–93.5	(224, 225)
$CH\equiv CCH_2—$	$CH\equiv CCH_2—$	106–107	(123)
$CH_3(CH_2)_4—$	$H—$	>77	(347)
$CH_3(CH_2)_4—$	$CH_3(CH_2)_4—$	64.8	(347)
$(C_2H_5)_2NCH_2CH_2—$	$H—$		(64, 288)
$(C_2H_5)_2NCH_2CH_2—$	$(C_2H_5)_2NCH_2CH_2$-		(64, 288)
$CH_3(CH_2)_6—$	$H—$	86.5	(347)
$CH_3(CH_2)_6—$	$CH_3(CH_2)_6—$	49.5	(347)
 $HOCH_2\underbrace{CH(CHOH)_3CH}_{O}—$	$H—$	177–187	(432)
 $HOCH_2\underbrace{CH(CHOH)_3CH}_{O}—$	 $HOCH_2\underbrace{CH(CH_2OH)_3CH}_{O}—$	ca. 245 (d.)	(442)
 $CH_3COOCH_2CH(CHOCOCH_3)_3CH$-	 $CH_3COOCH_2\underbrace{CHCHOCOCH_3CH}_{O}—$	227–230	(442)
		117–119	(222, 223)

aminoethyl) ethers of diethylstilbestrol and hexestrol to be inactive. However, Milla and Grumelli (288) found some activity for the hexestrol ether. This suggests the greater susceptibility of diethylstilbestrol derivatives to *in vivo* degradation, as might be expected from the unsaturated nature of the compounds. The

TABLE 10

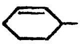
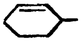
A. Ethers of hexestrol

$p\text{-}ROC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4OR'\text{-}p$

Compound		Melting Point	References
R	R'		
		°C.	
$CH_3—$	$H—$	119–121	(553)
		118.5	(382)
			(70)
$CH_3—$	$CH_3—$	144	(382)
$CH_3CH_2—$	$CH_3CH_2—$	133	(48)
			(233)
$CH_3(CH_2)_2—$	$CH_3(CH_2)_2—$	110	(48)
$(CH_3)_2CH—$	$(CH_3)_2CH—$	115	(48)
$CH_2{=}CHCH_2$	$CH_2{=}CHCH_2—$	81.5	(224, 226)
$CH_3(CH_2)_3—$	$H—$	105.5	(382)
$CH_3(CH_2)_3—$	$CH_3(CH_2)_3—$	107.5	(382)
$(CH_3)_2CHCH_2—$	$(CH_3)_2CHCH_2—$	109	(48)
$CH_3(CH_2)_4—$	$H—$	100.5	(382)
$CH_3(CH_2)_4—$	$CH_3(CH_2)_4—$	88.5	(382)
$(C_2H_5)_2NCH_2CH_2—$	$H—$		(288)
$(C_2H_5)_2NCH_2CH_2—$	$(C_2H_5)_2NCH_2CH_2—$		(64, 288)
$(CH_3)_2CH(CH_2)_2—$	$(CH_3)_2CH(CH_2)_2—$	83	(48)
$CH_3(CH_2)_5—$	$CH_3(CH_2)_5—$	73	(48)
$CH_3(CH_2)_7—$	$CH_3(CH_2)_7—$	66	(48)
$CH_3(CH_2)_9—$	$CH_3(CH_2)_9—$	57	(48)
$CH_3(CH_2)_{11}—$	$CH_3(CH_2)_{11}—$	79	(48)
$CH_3(CH_2)_{13}—$	$CH_3(CH_2)_{13}—$	65	(48)
$CH_3(CH_2)_{15}—$	$CH_3(CH_2)_{15}—$	72	(48)
$CH_3(CH_2)_{17}—$	$CH_3(CH_2)_{17}—$	92	(48)
		123–124	(222, 223)
$C_6H_5CH_2—$	$C_6H_5CH_2—$	219	(48)
$p\text{-}ClC_6H_4CH_2—$	$p\text{-}ClC_6H_4CH_2—$	194	(48)
			(48)
$C_6H_5(CH_2)_2—$	$C_6H_5(CH_2)_2—$	119	(48)
$C_6H_5(CH_2)_3—$	$C_6H_5(CH_2)_3—$	157	(48)
$C_6H_5CH{=}CH—$	$C_6H_5CH{=}CH—$	180	(48)
$1—C_{10}H_7CH_2—$	$1—C_{10}H_7CH_2—$	233	(48)
 $HOCH_2\underbrace{CH(CHOH)_3CH}_{O}—$	 $HOCH_2\underbrace{CH(CHOH)_3CH}_{O}—$	266–267	(443)
 $CH_3COOCH_2\underbrace{CH(CHOCOCH_3)_3CH}_{O}—$	 $CH_3COOCH_2CH(CHOCOCH_3)_3CH—$	186–188	(443)

B. Ether of dienestrol

$p\text{-}ROC_6H_4C({=}CHCH_3)C({=}CHCH_3)C_6H_4OR'\text{-}p$

Compound		Melting Point	References
R	R'		
		°C.	
		155–155.5	(223)

bis(carboxymethyl) ether of diethylstilbestrol is inactive (103). A therapeutically valuable preparation was claimed (27, 29) to have been obtained by dissolving 0.5 per cent of diethylstilbestrol dimethyl ether and 0.75 per cent of diethylstilbestrol in oil. The preparation was found to have high potency at therapeutic dosage, rapid as well as prolonged action, and no toxicity intramuscularly.

The ethers have, in general, been obtained by interaction of the phenol and an alkyl sulfate or halide. Schönberg and Mustafa (386) claimed the preparation of diethylstilbestrol di-*n*-propyl ether by reacting the phenol and diazomethane in ether and *n*-propyl alcohol. Gerber and Curtin (138) obtained only the dimethyl ether from the reaction. This result was substantiated by Wegand and Grisebach (540), although in repetition of the work Mustafa (300) claimed that he obtained micro quantities of the di-*n*-propyl ether. Few biological activities for ether derivatives have been quoted recently, though they have been given previously by Solmssen (454). Ethers which have been recently prepared or reprepared are listed in tables 9 and 10. The new diallyl ethers of diethylstilbestrol and hexestrol (224) have about $\frac{1}{250}$ the activity of diethylstilbestrol.

VI. VARIATION OF THE FUNDAMENTAL STRUCTURE OF DIETHYLSTILBESTROL, HEXESTROL, AND DIENESTROL

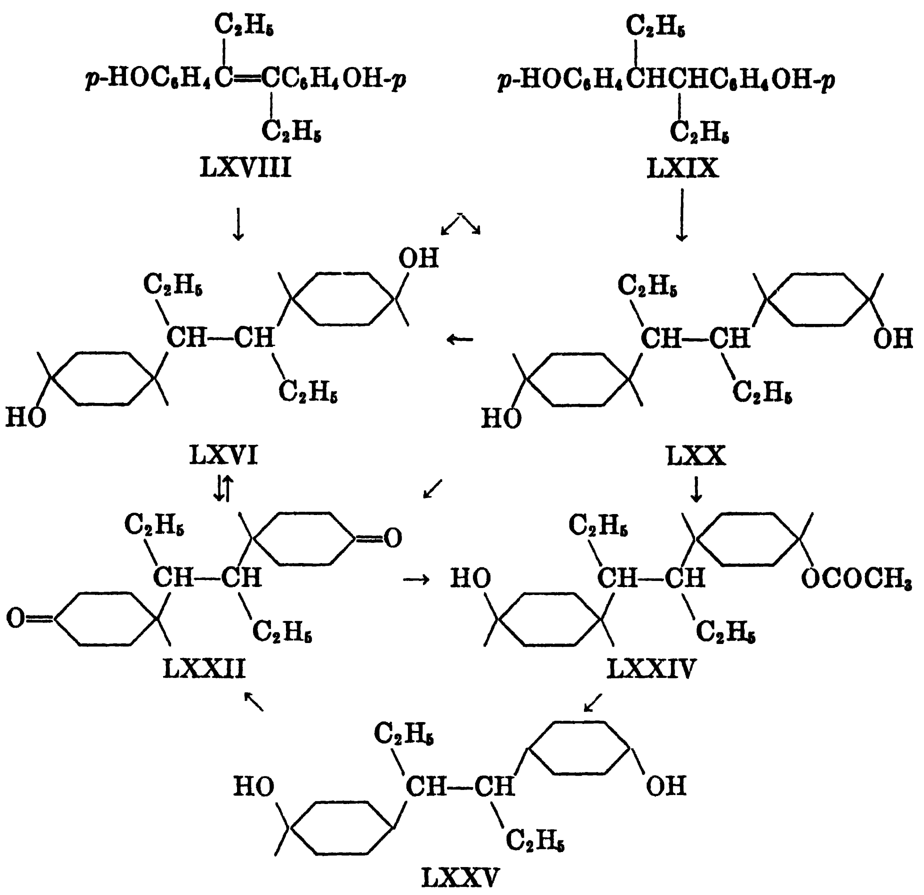
A. HYDROGENATED DERIVATIVES

1. Hydrogenation of exocyclic double bonds

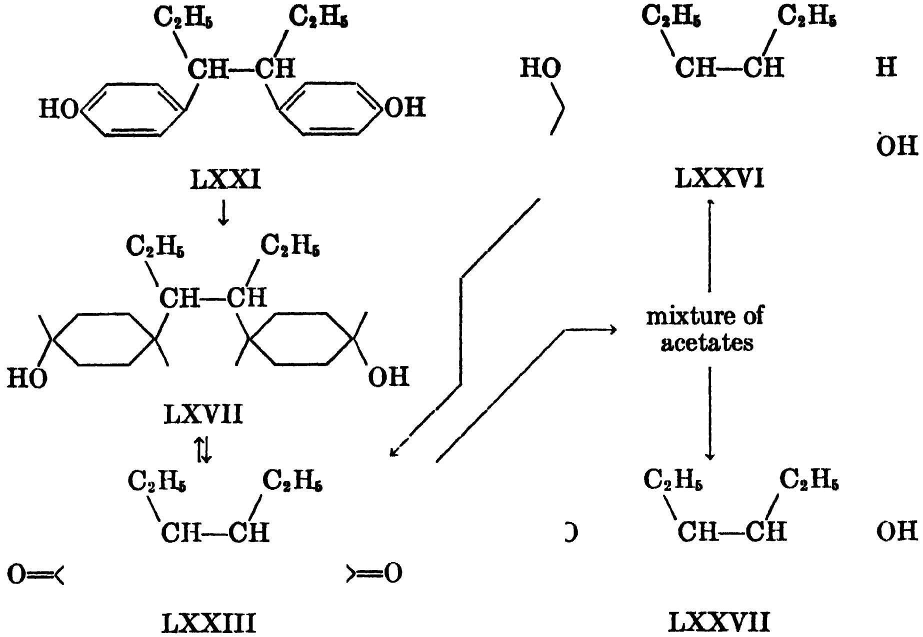
The hexestrols are dihydrodiethylstilbestrols or tetrahydrodienestrols; hence hydrogenation methods (293) have naturally been used to obtain hexestrol. *trans*-Diethylstilbestrol and its derivatives are hydrogenated in general to a mixture of racemic and *meso*-hexestrols, the former in preponderance; cis derivatives yield largely the meso dihydro compound with some racemic compound (455). Wessely and coworkers (231) obtained hexestrol dimethyl ether quantitatively from ψ-stilbestrol dimethyl ether. The mechanisms of these conversions are not fully understood. Campbell, Dodds, and Lawson (53) reported that the hydrogenation of dienestrol in acetone with a palladium catalyst gave a quantitative yield of hexestrol. Williams and Ronzio (556), however, found that in acetone and with 10 per cent palladium on charcoal and at atmospheric pressure a 72–77 per cent yield of *meso*-hexestrol and a 27 per cent yield of racemic hexestrol were obtained from dienestrol. Crystallization from benzene proved an excellent method of separating the isomers; the racemate remained in solution.

2. Hydrogenation of aromatic rings

Hoehn and Ungnade (174) hydrogenated diethylstilbestrol at 210°C. and under 265 atm. pressure with Raney nickel and obtained two isomeric octahydro compounds, melting at 92–94°C. and 144–145°C., together with a perhydrogenated derivative melting at 188–188.5°C. By a similar technique Ungnade and Ludutsky (515) obtained six perhydro compounds, two of which—LXVI, m.p. 189–190°C. (174, 274), and LXVII, m.p. 167°C. (254)—were known previously. The compound LXVI was assigned the racemic bridge structure, since hydro-



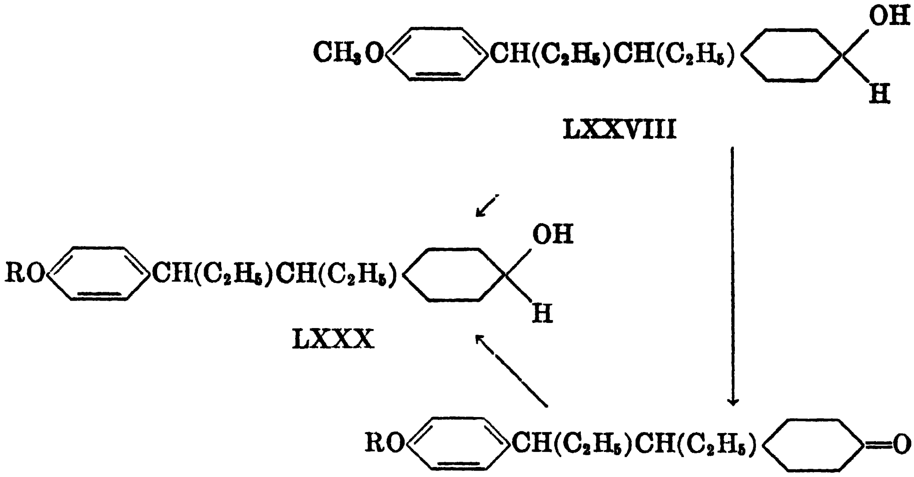
genation of diethylstilbestrol (LXVIII) with nickel was known to give racemic hexestrol. Reduction of racemic hexestrol (LXIX) with nickel also gave LXVI together with a new isomer (LXX), melting at 129–130°C. Analogously LXVII, obtained from *meso*-hexestrol LXXI (245), was assigned the meso bridge structure. The ketones LXXII and LXXIII, obtained by oxidation, will have the racemic and meso configurations, respectively. Reduction of LXXII with sodium in ethyl alcohol gave LXVI as the main product, indicating that the hydroxyl groups in the latter have the trans configuration (417). Inversion of LXX by sodium at 175°C. gave LXVI, but no LXVI was obtained by reduction of LXXII in acetic acid. Since inversion of *cis*-alkylcyclohexanols by sodium gives trans forms or cis-trans mixtures, the latter form predominating (529), and since only neutral or basic reduction of LXXII would favor the production of LXVI (417), the trans hydroxyl configuration of LXVI is confirmed and LXX will have at least one cis hydroxyl group. Ease of adsorption on sodium sulfate together with evidence from benzoylation indicated that the second hydroxyl group in LXX was trans. Catalytic reduction of LXXII using platinum in acetic acid gave a monoacetate (LXXIV), which with methylmagnesium iodide gave a



new perhydro isomer (LXXV). Evidence similar to the above indicated it to have cis-cis configuration for the hydroxyl group. Ungnade and Ludutsky repeated the hydrogenation of *meso*-hexestrol and obtained the isomer LXVII, m.p. 167°C., together with a new isomer (LXXVI), m.p. 124–125°C. On oxidation both these alcohols gave LXXIII. By the methods discussed LXVII was assigned the trans-trans configuration of the hydroxyl groups, LXXVI was assigned the cis-trans configuration, and the further isomer (LXXVII) was considered to have the cis-cis configuration.

Ungnade and Ludutsky (516) by partial hydrogenation of diethylstilbestrol at 210°C. and 265 atm. obtained from the mixture of products an octahydro compound melting at 147–148°C. Hydrogenation of this compound gave LXVI, indicating a trans hydroxyl and a racemic bridge in the octahydro compound. A second octahydro compound, m.p. 142–143°C., was also obtained and shown to be identical to that previously described by Hoehn and Ungnade (174) as melting at 144–145°C.; it was thought to be a meso compound. The octahydro compound described by Hoehn and Ungnade (174) as melting at 92–94°C. was found to be a complex of the compound melting at 142–143°C. and racemic hexestrol.

Wilds and McCormack (553), after failing to satisfactorily hydrogenate one ring of hexestrol or its monobenzoate, succeeded with hexestrol monomethyl ether and a chromium oxide catalyst (299); the phenolic ring was reduced to give LXXVIII. Oxidation of the crude hydrogenation product gave a 52 per cent yield of LXXIX (R = CH_3). Demethylation of LXXVIII gave a mixture from which two isomers of LXXX (R = H), melting at 183–184°C. and 134–135°C., were obtained, the latter preponderating. The perhydro compound (LXVII)


CH$_3$O
CH(C$_2$H$_5$)CH(C$_2$H$_5$)
OH
H
RO
CH(C$_2$H$_5$)CH(C$_2$H$_5$)
OH
H
RO
CH(C$_2$H$_5$)CH(C$_2$H$_5$)
=O

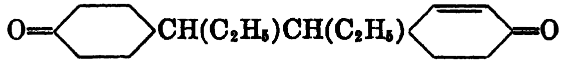
LXXVIII

LXXX

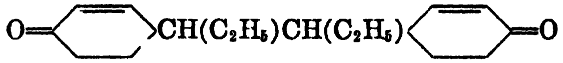
LXXIX

previously mentioned was obtained by Wilds and McCormack by hydrogenating both isomers (LXXX: R = H). Hydrogenation of LXXIX (R = CH_3) under neutral conditions followed by demethylation gave largely LXXX (R = H), m.p. 134–135°C.; under acid conditions LXXX (R = H), m.p. 183–184°C., was the main product. This suggested a cis hydroxyl group configuration for the higher-melting isomer and a trans configuration for the lower-melting one. However, by hydrogenation of hexestrol in methanol with Raney nickel at 210°C. and 5300 lb. pressure, Ungnade and Tucker (518) isolated an octahydro compound which proved identical with LXXX (R = H) melting at 134–135°C. Further hydrogenation of this gave LXVII which, however, in view of the results of Wilds and McCormack, was not evidence for the trans configuration of the octahydro compound. The compound was shown not to be identical to the octahydro compound, m.p. 142–143°C., previously obtained by Ungnade and Ludutsky and thought to be a meso isomer (516). The position was resolved by a reinvestigation of the racemic octahydro compounds by Ungnade and Tucker (519). Hydrogenation of racemic hexestrol monomethyl ether in dioxane at 250°C. and 440 atm. pressure over copper chromite gave three products melting at 146–147°C., 141–142°C., and 47–50°C. The first two substances were regarded as racemic octahydro compounds, the one melting at 141–142°C. being identical to that melting at 142–143°C. and previously considered to have the meso configuration. The substance melting at 47–50°C. was presumed to be a mixture of these two octahydro compounds. The actual configuration of the hydroxyl groups was not established. The biological activities of these perhydrogenation products has not been extensively investigated but appears to be very dependent on configuration. A perhydro compound examined by Brownlee and Green (37) was found to be almost inactive, but the compound LXXX (R = H), m.p. 183–184°C., was active at 500 micrograms and its isomer was active at 10 micrograms in rats when given subcutaneously.

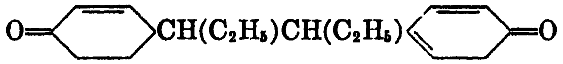
Ungnade and Tucker (519a), following the work of Schoeller, Inhoffen, Steinruck, and Hoss (385), obtained a series of diketones (LXXXI, LXXXII, and LXXXIII) of both racemic and meso types.



LXXXI



LXXXII



LXXXIII

The ketones LXXII and LXXIII, previously mentioned, were brominated using *N*-bromosuccinimide; dehydrobromination with collidine gave the unsaturated ketones in good yield. Isolation of LXXXIII showed that even *N*-bromosuccinimide (383) can attack a tertiary carbon atom. The ketones had no detectable androgenic activity.

Oxidation of *meso*- and racemic hexestrols with lead tetraacetate gave the corresponding forms of 3,4-bis(3,3-diacetoxy-4-oxo-1,5-cyclohexadien-1-yl)hexane (548); hydrogenation and subsequent hydrolysis gave the 3,4-bis(3,4-dihydroxyphenyl)hexanes.

B. VARIATION OF AROMATIC SUBSTITUTION

Variation of the substitution of the aromatic rings of the three stilbene estrogens, with regard to the effect on estrogenic activity, has been intensively studied (tables 11, 12, and 13).

The para hydroxyl groups are essential to high activity. α,α'-Diethylstilbene required about 50 mg. for 50 per cent response (214); the hexestrol analog, 3,4-diphenylhexane (214), is rather more active and required less than 1 mg. for 50 per cent response. 3,4-Diphenylhexadiene required 10 mg. for 100 per cent response and 5 mg. for 60 per cent response (103). These compounds are presumably hydroxylated *in vivo* and this is probably responsible for the lower activity of the unsaturated compounds, these being more susceptible to degradation in the body. The introduction of even one para hydroxyl group considerably enhances activity (37). Removal of hydroxyl groups to meta or ortho positions (48) considerably decreases the activity of the parent substances.

Jenkins and Wilkinson (216) prepared 4'-amino-α,α'-diethyl-4-hydroxy-

$$p\text{-}HOC_6H_4C(C_2H_5) = C(C_2H_5)C_6H_4NH_2\text{-}p$$

LXXXIV

$$p\text{-}HOC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4NH_2\text{-}p$$

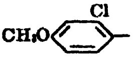
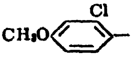
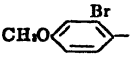
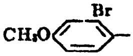
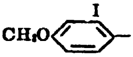
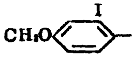
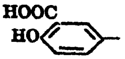
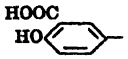
LXXXV

stilbene (LXXXIV) as a cis-trans mixture; in the final stage of the synthesis demethylation of the methyl ether of LXXXIV proved difficult. This compound

TABLE 11

Compounds related to diethylstilbestrol with variation of aromatic substitution

$RC(C_2H_5)=C(C_2H_5)R'$

Compound		Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
R	R'	°*C.*		
C_6H_5—	C_6H_5—	71 (trans form)	ca. 50 mg. (50%)	(214)
p-HOC_6H_4—	C_6H_5—		0.025	(37)
			0.017† (Diethylstilbestrol = 1)	(37)
p-$(C_2H_5)_2N(CH_2)_2OC_6H_4$—	C_6H_5—	240–245/5 mm. (b.p.)		(277)
Hydrochloride................		195		(277)
p-HOC_6H_4—	*p*-$H_2NC_6H_4$—	134–137 (cis-trans mixture)	0.1 mg.*	(216)
			0.01 mg.* (50%)	(216)
		180–183 (trans form)		(541)
p-HOC_6H_4—	*m*-$H_2NC_6H_4$—	163–164	1 mg.*	(216)
p-$CH_3OC_6H_4$—	*p*-$[\overset{-}{Cl}\overset{+}{N}H_3C(=NH)]C_6H_4$—	202–203	1 mg.* (inactive)	(216)
m-HOC_6H_4—	*m*-HOC_6H_4—	188		(544)
o-HOC_6H_4—	*o*-HOC_6H_4—	159–160		(544)
C_6H_5—	*p*-$CH_3COC_6H_4$—	205–210/10 mm. (b.p.)	Inactive	(52)
p-HOC_6H_4—	*p*-$CH_3COC_6H_4$—	144.5–146.5	500-1000	(19)
		Impure	50	(19)
p-$CH_3OC_6H_4$—	*p*-$C_2H_5COC_6H_4$—	176–178/0.06 mm. (b.p.)	1 mg.*	(216)
p-$CH_3COOC_6H_4$—	*p*-$CH_3COOCH_2COC_6H_4$—	133.2–134	100	(19)
p-$CH_3OC_6H_4$—	*p*-$CH_3SC_6H_4$—	107–108	5*‡	(321)
p-$CH_3SC_6H_4$—	*p*-$CH_3SC_6H_4$—	132–132.5	40*‡	(321)
		105.5–106.5 (trans form)	100*‡	(322)
		88–89/0.07 mm. (b.p.) (cis form)	1 mg.*‡	(322)
		114.5–115 (trans form)	100*‡	(322)
		87–89/0.04 mm. (b.p.) (cis form)	1 mg.*‡	(322)
			200*‡ (trans form)	(322)
		108–110/0.02 mm. (b.p.) (cis form)	1 mg.*‡	(322)
p-HOC_6H_4—	*p*-$HOOCC_6H_4$—	143–146.5 (trans form)		(19)
		144–146 (trans form)	20	(303)
			40†	(303)
		143–146 (trans form)		(557)
p-$CH_3OC_6H_4$—	*p*-$HOOCC_6H_4$—	116–117	1 mg. (inactive)	(303)
p-HOC_6H_4—	*m*-$HOOCC_6H_4$—	180–183.5	1 mg. (inactive)	(303)
		270–275	100 (inactive)	(546)

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* In mice.

† Orally.

‡ Administered in two portions.

TABLE 12

Hexestrol and dienestrol analogs with variation of aromatic substitution

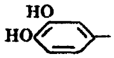
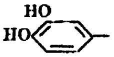
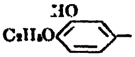
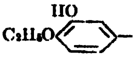
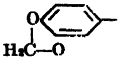
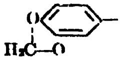
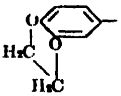
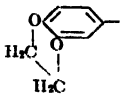
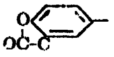
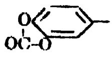
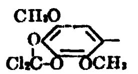
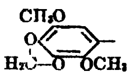
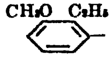
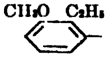
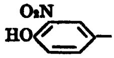
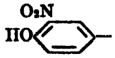
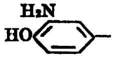
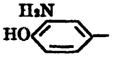
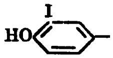
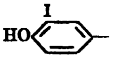
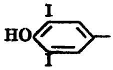
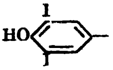
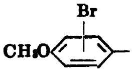
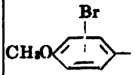
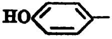
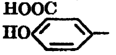
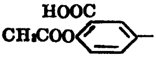
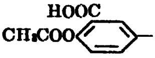
Compound		Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
R	R′			
A. Hexestrol analogs: $RCH(C_2H_5)CH(C_2H_5)R'$				
		°C.		
C_6H_5—	C_6H_5—	89 (meso form)	<1 mg. (50%)	(214)
		89–91		(538)
o-HOC_6H_4—	*o*-HOC_6H_4—	155 (meso form)		(48)
			0.1 mg.	(45)
p-HOC_6H_4—	C_6H_5—	143-144 (meso form)		(538)
		152-153/0.07 mm. (b.p.) (racemic form)		(538)
		233–236 (meso form)		(548)
		235 (d.) (meso form)		(376)
		230–235 (d.) (meso form)		(407)
				(142, 143)
		138 (racemic form)		(548)
Diacetate		167.5–168 (meso form)	Some activity at 500	(548)
		166–167 (meso form)		(407)
		133–134 (meso form)		(376)
		174–175 (meso form)		(403, 407)
				(233)
		175 (meso form)		(48)
		—		(233)
		186–187 (meso form)		(403, 407)
		157 (meso form)		(48)
		298–300/13 mm. (b.p.) (racemic form)		(48)
		163 (meso form)		(353)
		109 (racemic form)		(353)
p-HOC_6H_4—	*p*-$H_2NC_6H_4$—	186–188 (meso form)	20	(19)
p-$H_2NC_6H_4$—	*p*-$H_2NC_6H_4$—	132–134 (meso form)		(258)
		136–137 (meso form)		(131)
				(191)
		80 (racemic form)		(131)
p-$HOC_6H_4C(C_2H_5)(OH)CH(C_2H_5)C_6H_4NH_2$-*p*		181–182	1 mg.*	(216)
			0.1 mg.* (78%)	(216)
			0.01 mg.* (inactive)	(216)
p-BrC_6H_4—	*p*-BrC_6H_4—	168 (meso form)		(131)
p-$O_2NC_6H_4$—	*p*-$O_2NC_6H_4$—	170 (meso form)		(131)
		Oil (racemic form)		(131)

TABLE 12—*Concluded*

Compound		Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
R	R'	°C.		
		222 (meso form)	100	(169)
			10 (inactive)	
		258 (meso form)	5	(169)
			1 (inactive)	
		138–139 (meso form)	100	(169)
			10 (66%)	(169)
			5 (33%)	(169)
			1 (inactive)	(169)
		234 (d.)	100 (inactive)	(169)
		179–181		(510, 511, 512)
p-$CH_3SC_6H_4$—	p-$CH_3SC_6H_4$—	(153 meso form)	Inactive	(200)
		155–156 (meso form)		(49)
		62–63 (racemic form)	200*‡	(321)
p-HOC_6H_4—	p-$CH_3COC_6H_4$—	159–160 (meso form)	100	(19)
p-$CH_3COOC_6H_4$—	p-$CH_3COOCH_2COC_6H_4$—	152–153.5 (meso form)	500–1000	(19)
		Impure meso form	100	(19)
p-HOC_6H_4—	p-$HOOCC_6H_4$—	171.5–172.5 (meso form)		(19)
		Isomer mixture	50–70 (60%)	(303)
		166–168 (meso form)		(557)
		126–128 (racemic form)		(19)
p-$HOC_6H_4C(C_2H_5)(OH)CH(C_2H_5)C_6H_4COOH$-p..		144–146 (meso form)	100 (inactive)	(303)
		283–285 (meso form)	100 (inactive)	(546)
		>350 (meso form)	100 (inactive)	(546)
B. Dienestrol analogs: $RC(=CHCH_3)C(=CHCH_3)R'$				
C_6H_5—	C_6H_5—	101	>1 mg., <10 mg. (50%)	(214)
			10 mg.	(103)
			5 mg. (60%)	(103)
p-$CH_3SC_6H_4$—	p-$CH_3SC_6H_4$—	141		(201)

* In mice.

‡ Administered in two portions.

was found to produce 50 per cent response in mice at 0.01 mg. in contrast to 7.5 micrograms for 50 per cent response in the rat reported earlier by Rubin and Wishinsky (370). The results of the latter are more difficult to understand in view of the proof by Weiss (541) that their compound was in fact the cis isomer,

TABLE 13

Diethylstilbestrol, hexestrol, and dienestrol analogs with hydrocarbon group substitution of the aromatic rings

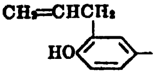
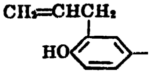
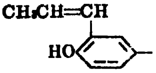
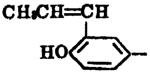
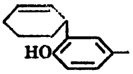
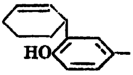
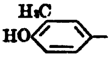
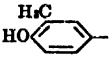
Compound		Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
R	R'			
A. Diethylstilbestrol analogs: $RC(C_2H_5)=C(C_2H_5)R'$				
		°C.		
		103–104		(224, 225)
			6–7§	(224)
			10–20*§	(224)
		120–121		(224, 225)
			0.1–0.2*§	(224)
		154–156		(222, 223)
B. Hexestrol analogs: $RCH(C_2H_5)CH(C_2H_5)R'$				
		145		(26, 312, 313)
			1.5 (90%)	(313)
			1.0 (70%)	(313)
			0.6 (30%)	(313)
			15† (65%)	(313)
		165–166	0.005 mg.	(103)
			0.001 mg. (inactive)	(103)
Diacetate		132		(26, 312, 313)
			15 (95%)	(313)
			5 (75%)	(313)
			2.5 (10%)	(313)
			10† (70%)	(313)
			5† (30%)	(313)
			2.5† (inactive)	(313)
Dipropionate		115		(312, 313)
			15 (60%)	(313)
			10† (90%)	(313)
			5† (50%)	(313)
			2.5† (inactive)	(313)
				(26)
Di-*n*-butyrate		100–101		(312, 313)
			15† (60%)	(313)
				(26)
Dipalmitate		68–69		(313)
Bis(acid succinate)		198–200	15	(313)
			5† (30%)	(313)
Bis(ethyl carbonate)		138	50	(313)
			15† (70%)	(313)
Bis(methyl carbonate)		148–149		(313)
Dibenzoate		199–200	5† (85%)	(313)
Bis(*m*-sulfobenzoate, disodium salt		ca. 300 (d.)	6	(313)
			10† (50%)	(313)

TABLE 13—*Continued*

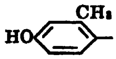
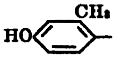
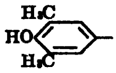
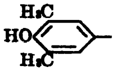
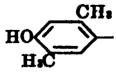
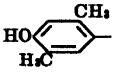
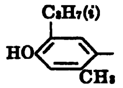
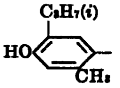
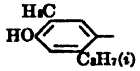
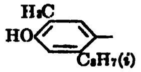
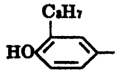
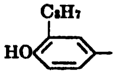
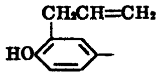
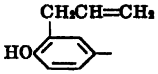
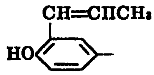
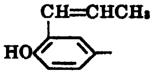
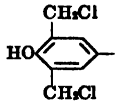
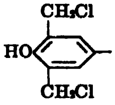
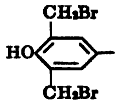
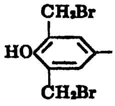
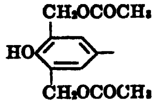
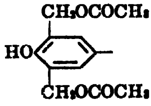
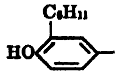
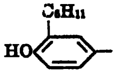
Compound		Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms Unless Indicated Otherwise	References
R	R'	°C.		
		214–215 (meso form)	0.001 mg.	(103)
			0.0003 mg. (inactive)	(103)
		218–219 (meso form)		(403)
		191–192		(221)
		216	5	(310)
			2 (ca. 100%)	(310)
			1 (ca. 100%)	(310)
Diacetate		163		(310)
Dibenzoate		204		(310)
		177	50 (10%)	(310)
		171	50 (inactive)	(310)
		123.5–124.5		(224, 226)
			> 0.5*§	(224)
		107		(224, 226)
			<4*§	(224)
			1-2§	(224)
		153–154		(224, 226)
			<4*§	(224)
			<1§	(224)
		156–159		(221)
				(221)
		137.5–139		(221)
		195–197	50 (10%)	(309)

TABLE 13—*Continued*

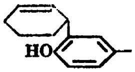
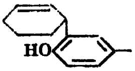
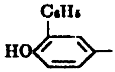
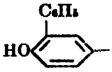
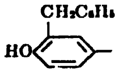
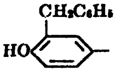
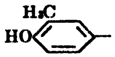
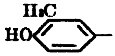
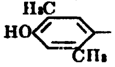
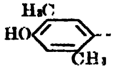
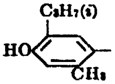
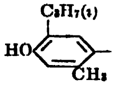
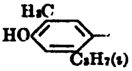
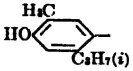
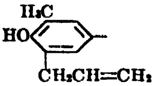
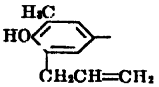
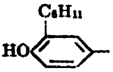
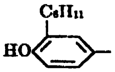
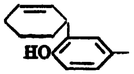
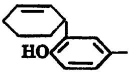
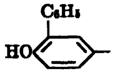
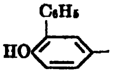
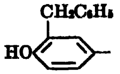
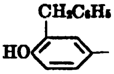
Compound		Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
R	R'			
		°C.		
		169-171		(222, 223)
		219-221 (d.)	50 (10%)	(308)
		169-171	50 (inactive)	(308)
C. Dienestrol analogs: RC(=CHCH$_3$)C(=CHCH$_3$)R'				
		187-189		(313, 26)
			5	(313)
			2.5 (30%)	(313)
			15† (10%)	(313)
			5† (inactive)	(313)
		189-190	0.01 mg.	(103)
			0.005 mg. (75%)	(103)
Diacetate		166-168		(26, 312, 313)
			15 (80%)	(313)
			15† (65%)	(313)
Dipropionate		138-139		(26, 312, 313)
			15 (inactive)	(313)
			15† (85%)	(313)
			10† (30%)	(313)
			5† (inactive)	(313)
Di-*n*-butyrate		123-124	15† (15%)	(313)
		206		(310)
		169		(310)
		163		(310)
		Gum	100† (35%)	(542)
Diacetate		125-126	100† (25%)	(542)
Dipropionate		114-115	100† (20%)	(542)
		177-178		(309)

TABLE 13—*Concluded*

Compound		Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
R	R'			
		°C.		
				(223)
		202–204 (d.)		(308)
				(308)

* In mice.
† Administered orally.
§ Diethylstilbestrol = 250.

as this would be expected to be inactive. Removal of the amino group to the meta position (216) further decreased the activity relative to LXXXIV. Biggerstaff and Wilds (19) obtained the hexestrol analog (LXXXV) and found it active at 20 micrograms in the rat. The methyl ether of LXXXV was relatively easy to demethylate. Although Jenkins and Wilkinson found no antiestrogenic properties for their amino compounds, Danneberg and Schmahl (85) reported *p*-aminostilbene and *p*-aminoazobenzene, as well as their *N*-acetyl and *N*-methyl derivatives, to be effective inhibitors of estrus. It appears that the amino group, in spite of its hydrogen-bonding capacity, cannot replace a hydroxyl group in an estrogen and, in fact, may result in an estrus inhibitor. This is probably due to the steric dissimilarity between the two groups.

Hughes and Thompson (200) reduced *p*-(methylthio)propiophenone with aluminum isopropoxide; dehydration of the indefinite product by potassium bisulfate at 180–190°C. gave an 85 per cent yield of thioanethole. This yield was obtained only when air was present during the distillation of the reduction product prior to dehydration. Conversion to thioanethole hydrobromide and reaction of this with phenylmagnesium bromide and cobaltous chloride gave finally a 12 per cent yield of dithiohexestrol dimethyl ether (LXXXVI).

$$p\text{-}CH_3C_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_5SCH_3\text{-}p$$

LXXXVI

Buu-Hoï and Hoán (49) claimed a 25 per cent yield of LXXXVI by treatment of thioanethole hydrochloride with reduced iron and water at 95°C. The compound was found inactive (200), and there is evidence that replacement of phenol groups by thiophenol groups reduces or abolishes biological activity (49). While the thiophenol analog of hexestrol would be expected to show some estrogenic activity, LXXXVI is presumably inactive because of the difficulty of *in vivo* demethylation. Thio ethers are well known to be very difficult to dealkylate (43, 199), and LXXXVI cannot be demethylated by pyridine hydrochloride or hydrogen iodide or bromide in acetic acid. Contrary to these results, Oki (321) found the racemic form of LXXXVI active in mice at 200 micrograms. LXXXVII, the thio analog of diethylstilbestrol dimethyl ether, was active at 40 micrograms and the monothio analog (LXXXVIII) was active at 5 micrograms.

$$p\text{-}CH_3SC_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_4SCH_3\text{-}p$$

LXXXVII

$$p\text{-}CH_3OC_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_4SCH_3\text{-}p$$

LXXXVIII

Replacement of one hydroxyl group of diethylstilbestrol by a carboxyl group, as in LXXXIX (303), gave a product active at 20 micrograms; the methyl ether was effectively inactive. The hexestrol analog (XC) was 60 per cent active at 50–70 micrograms (303). Extending the separation of hydrogen-bonding groups by

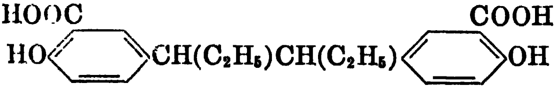
$$p\text{-}HOC_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_4COOH\text{-}p$$

LXXXIX

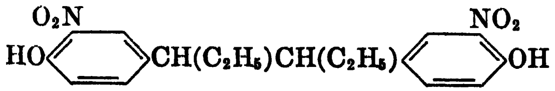
$$p\text{-}HOC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4COOH\text{-}p$$

XC

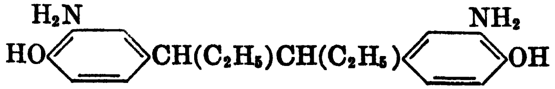
the use of a carboxyl group is apparently permissible, but it leads to a decrease of activity. The electrostatic nature of the hydrogen bond suggests that some degree of elasticity in the separation of the hydrogen-bond-forming groups is permissible. 3,4-Bis(3-carboxy-4-hydroxyphenyl)hexane (XCI) (546), prepared by the Marasse reaction from hexestrol, was inactive at 100 micrograms. Probably intramolecular hydrogen bonding is responsible for the diminished activity. Intramolecular hydrogen bonding would appear to account for the relative activities of 3,4-bis(4-hydroxy-3-nitrophenyl)hexane (XCII) and its amino analog (XCIII); the former was active at 100 micrograms and the latter at 5 micrograms (169).



XCI



XCII



XCIII

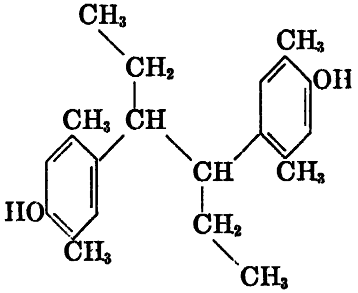
Biggerstaff and Wilds (19) prepared and tested a series of compounds related to diethylstilbestrol and hexestrol in which a hydroxyl group was replaced by an acetyl, acetoxy, or acetoxyacetyl group. 4′-Acetyl-α,α′-diethyl-4-hydroxystilbene (XCIV) was active at 500–1000 micrograms, and the impure compound was still more active, possibly owing to the presence of the carboxylic acid

$$p\text{-}HOC_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_4COCH_3\text{-}p$$

XCIV

analog; the hexestrol analog was some five times more active than XCIV. These orders of activity were reversed in the 4-acetoxy-4′-(acetoxyacetyl) compounds. Presumably, these compounds are biochemically modified *in vivo.* 4′-Acetyl-α,α′-diethylstilbene was inactive (52).

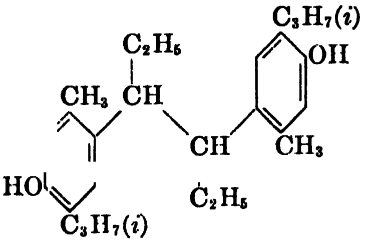
The introduction of alkyl or other hydrocarbon groups into the aromatic rings of the three principal stilbene estrogens has interesting effects on estrogenic activity (table 13). The introduction of 3-methyl groups into the hexestrol and dienestrol molecules does not drastically affect estrogenic potency (313). Following the general rule, the esters of 3,3′-dimethylhexestrol are more active subcutaneously than orally; even orally they are more active than estrone, similarly administered. In the analogous dienestrol derivatives the diacetate and parent phenol are more active subcutaneously, but the dipropionate is much more active when given orally. These compounds were reported as being relatively nontoxic; the median lethal dose of diethylstilbestrol in mice is 18 mg., but for 3,4-bis(3-methyl-4-acetoxyphenyl)-2,4-hexadiene and 3,4-bis(3-methyl-4-propionoxyphenyl)hexane the value was found to be 36 mg. The introduction of a second 2-methyl group into the rings, as in XCV, increased the activity; the dimethyl-substituted compound (XCV) is almost fully active at 1 microgram (310).



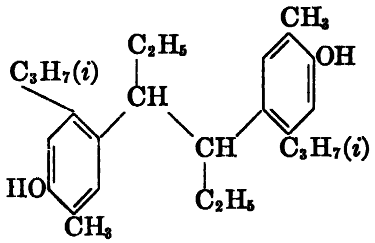
XCV

Presumably this tetramethyl compound has the configuration shown in formula XCV; the 2-methyl groups result in the "completion" of a new "ring system." Correcting earlier work (93, 94, 95, 204, 205, 206, 551, 552), Djerassi, Rosenkranz, Romo, Pataki, and Kaufmann (92) found that the introduction of a 1-methyl group into estrone decreased the activity of the latter by one-half. Apparently this type of methyl substitution does not abolish activity in the natural estrogens.

3,4-Bis(4-hydroxy-5-isopropyl-2-methylphenyl)hexane (XCVI) and 3,4-bis-(4-hydroxy-2-isopropyl-5-methylphenyl)hexane (XCVII) have little activity.



XCVI



XCVII

The 5-isopropyl group will have considerable steric effect on the hydroxyl group, impairing its biochemical function; the 2-isopropyl group possibly has an undesirable effect on molecular thickness.

The 3,3′-diallyl-, 3,3′-dipropenyl-, and 3,3′-dipropylhexestrols and the 3,3′-diallyl- and 3,3′-dipropenyldiethylstilbestrols (224) have negligible activities. Cyclohexyl, phenyl, and presumably benzyl groups introduced into the 3,3′-positions of hexestrol or dienestrol (308) similarly decrease the activity of the parent compounds to negligible values. These results suggest a limit of three to four carbon atoms in extending the molecule by alkyl substitution in the 3,3′-positions.

C. VARIATION OF THE ALIPHATIC PORTION

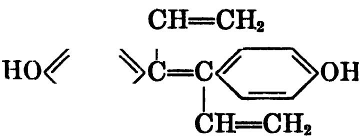
1. Variation of the α,α′-alkyl groups

The constitution of the aliphatic portion of diethylstilbestrol, hexestrol, and dienestrol is optimum for estrogenic activity in the stilbene-type estrogen (456).

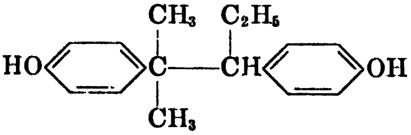
Removal of the ethyl groups from diethylstilbestrol (104) or from hexestrol (45) leads essentially to removal of activity. Replacement of ethyl groups by methyl or higher alkyl groups decreases the activity (45, 48); the higher the alkyl group, the greater the decrease. α′-Isopropyl-α-methylstilbestrol (XCVIII) (291) is exceptional, being almost as active as diethylstilbestrol.

HO<   \>$C(CH_3)=C[CH(CH_3)_2]$ >OH

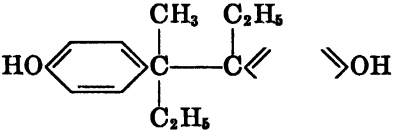
XCVIII



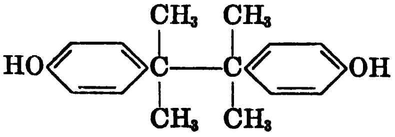
XCIX



C



CI



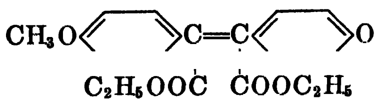
CII

More recently, Dodds, Huang, Lawson, and Robinson (103) found 3,4-bis(*p*-hydroxyphenyl)-1,3,5-hexatriene ("trienestrol") (XCIX) to be as active as diethylstilbestrol when given subcutaneously to the rat. Trienestrol had also been prepared earlier by Freiman (134). The methods of synthesis differed slightly, as Dodds, Huang, Lawson, and Robinson converted dienestrol to its 4,4′-bis(methoxycarbonyloxy) derivative and this into the 2,5-dibromo compound by the action of bromine in chloroform at 0°C., while Freiman obtained a 2,5-dibromo compound by bromination of diethylstilbestrol dipropionate with *N*-bromosuccinimide in carbon tetrachloride. Both methods obtained trienestrol by dehydrohalogenation of the bromo compounds in *N*-diethylaniline and subsequent hydrolysis. Replacing one ethyl group of hexestrol by two methyl groups gives a quite active compound (C); adding one methyl group to the aliphatic portion of hexestrol as in CI has little effect on activity (103). However, replacement of the ethyl groups by four methyl groups (191), as in CII, effectively abolishes activity.

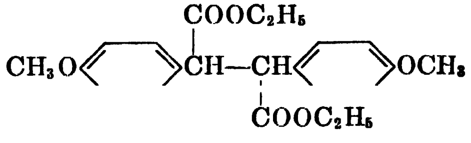
The aliphatic portion of diethylstilbestrol appears to be optimum because it confers the appropriate solubility, adsorption capacity, and stereochemistry on the molecule. With the data available it is not possible to separate the adsorption and stereochemical factors. α′-Isopropyl-α-methylstilbestrol could owe its activity to an improved steric or adsorption factor caused by the isopropyl group. While 4,4′-dihydroxystilbene will have the unfavorable planar configuration, 4,4′-dihydroxybibenzyl has the favorable configuration, as previously mentioned. The meso dialkyl analogs of hexestrol similarly have appropriate stereochemistry. The functions of the alkyl groups in the hexestrol series appear to be to impart rigidity to the favorable configuration, preventing planarity, and to aid adsorption. The low activity of 4,4′-dihydroxystilbene is probably due to absence of molecular thickness and in 4,4′-dihydroxybibenzyl to lack of rigidity and adsorption capacity. The inactivity of CII is presumably due to an undesirable steric effect and indicates that estrogenic activity is sensitive to stereochemical change arising from the aliphatic portion.

2. *Other variations in the α,α′ substituents*

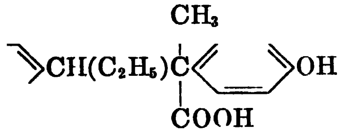
Hoch (173) condensed ethyl α-bromo-*p*-methoxyphenylacetate by means of sodium amide in ether and obtained diethyl bis(*p*-methoxyphenyl)maleate (CIII) together with a little diethyl α,β-bis(*p*-methoxyphenyl)succinate (CIV).



CIII

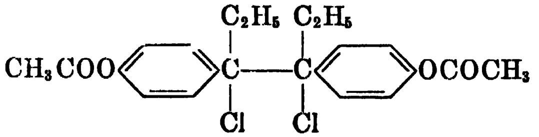


CIV

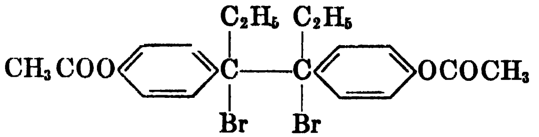


CV

With ethyl α-bromophenylacetate, 45 per cent of diethyl diphenylmaleate, 10 per cent of diethyl diphenylfumarate, and 4 per cent and 1 per cent of diethyl diphenylsuccinates, melting at 141° and 84°C., respectively, was obtained. The phenol anhydride and analogs from CIII were found to be inactive; this may be anticipated in view of the cis relationship of the aromatic rings. Attempts to isomerize CIII to the fumarate failed. By hydrolysis and demethylation CIV was converted to the phenol acid and, despite its being a racemate, was claimed to be estrogenically active. Huang and Tatt (189) confirmed that Hoch's compound was the racemate and they also obtained the meso form; both isomers were found to be effectively inactive, a result probably related to water solubility. The related compound CV is active at 20 micrograms (202), but the dimethyl ether is inactive at 500 micrograms. Presumably this compound also has high translocatability, which may result in elimination before extensive demethylation can occur. Replacement of one ethyl group of hexestrol dimethyl ether by an acetyl group (41, 539) results in activity at 0.01 mg.; the stereoisomer was inactive at 1 mg. The similar introduction of the cyano group leads to activity at 1 mg. (539). Oki (320) replaced the ethyl groups of diethylstilbestrol by halogen atoms and found the chlorine derivatives to have the optimum effect; α,α′-dichloro-4,4′-dimethoxystilbene was active subcutaneously in mice at 200 micrograms and the chloro-iodo compound had twice this activity. It appears that the considered specificity of ethyl groups is not in fact the case. However, Henne and Bruylants (164) found that replacement of the ethyl groups of hexestrol dimethyl ether by chlorine or bromine atoms led to inactivity, although CVI and CVII were active at 25 micrograms. The converse of these results might



CVI



CVII

have been expected, since CVI and CVII simulate the tetramethyl compound (CII), which is inactive.

Oki and coworkers, investigating the effect of molecular thickness on estrogenic activity, synthesized a series of compounds related to diethylstilbestrol and hexestrol in which the ethyl groups were replaced by methylthio, alkoxy, or methylamino groups. 1,2-Bis(*p*-methoxyphenyl)-1,2-bis(methylthio)ethylene (CVIII) was obtained by passing gaseous hydrogen chloride into anisoin and methanethiol in acetic acid (325). Hydroanisoin gave the hexestrol analog

$$p\text{-}CH_3OC_6H_4C(SCH_3){=}C(SCH_3)C_6H_4OCH_3\text{-}p$$

CVIII

$$p\text{-}HOC_6H_4CH(SCH_3)CH(SCH_3)C_6H_4OH\text{-}p$$

CIX

$$p\text{-}CH_3OC_6H_4CH(C_2H_5)CH(SCH_3)C_6H_4OCH_3\text{-}p$$

CX

$$p\text{-}HOC_6H_4CH(OCH_3)CH(OCH_3)C_6H_4OH\text{-}p$$

CXI

$$p\text{-}HOC_6H_4CH(OC_2H_5)CH(OC_2H_5)C_6H_4OH\text{-}p$$

CXII

$$p\text{-}CH_3OC_6H_4CH(NHCH_3)CH(NHCH_3)C_6H_4OCH_3\text{-}p$$

CXIII

$$p\text{-}HOC_6H_4CH(C_2H_5)CH(NHCH_3)C_6H_4OH\text{-}p$$

CXIV

$$p\text{-}HOC_6H_4CH(C_2H_5)CH(OCH_3)C_6H_4OH\text{-}p$$

CXV

$$p\text{-}CH_3OC_6H_4CHOHCHOHC_6H_4OCH_3\text{-}p$$

CXVI

$$[p\text{-}CH_3OC_6H_4CH(\overset{+}{N}CH_3){=}CHC_6H_5]_2I_2^-$$

CXVII

(CIX) (521). CVIII was active at 10 micrograms, but the hexestrol analog (CIX), in spite of having free hydroxyl groups, was active only at 40 micrograms. The oxygen analogs (CXI and CXII) were obtained by alkylation of hydroanisoin (CXVI) with an alkyl iodide and silver oxide, followed by demethylation. CXI was active at 0.5 microgram; CXII was active at 10 micrograms (487, 523). The nitrogen analog (CXIII), active at 1000 micrograms, was obtained by reduction of anisil monoxime monohydrazone with sodium amalgam in alcohol. Conversion of the diamino compound obtained to the di-*N*-benzylidene derivative, followed by treatment with methyl iodide at 100°C., gave the methiodide (CXVII). Hydrolysis and demethylation yielded CXIII (488). Although CXI showed high activity, this was only 5 per cent of that of hexestrol similarly tested. Steric and adsorption factors are probably responsible for the variation of activities in these compounds. The monoethyl compounds CX (522) and CXV (485) were less active than CIX and CXI, respectively, but CXIV (486), as the dimethyl ether, was more active than CXIII (488). Niederl and Dexter (307) also obtained CXIII and the free phenol and reported their hydrochlorides inactive at 100 micrograms.

3. *Variation of the linking of the aromatic rings*

Nomura (315, 316) found CXVIII to have some activity at 60 micrograms.

$p\text{-}CH_3OC_6H_4CH(C_2H_5)N(C_2H_5)C_6H_4OCH_3\text{-}p$

CXVIII

$p\text{-}HOC_6H_4SC_6H_4OH\text{-}p$

CXIX

$p\text{-}CH_3OC_6H_4CH(C_2H_5)SCH(C_2H_5)C_6H_4OCH_3\text{-}p$

CXX

$p\text{-}HOC_6H_4SSC_6H_4OH\text{-}p$

CXXI

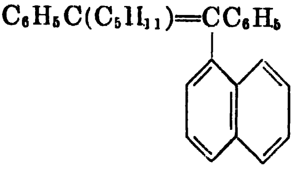
Chatten and Huston (65) found 4,4′-dihydroxydiphenyl sulfide (CXIX) active, but the corresponding disulfide (CXVII) was inactive; CXX, like CXIX, was also active at 100 mg. The authors considered these results to support the theory of Erlenmeyer (120, 121) that the sulfur atom is isosteric with the —CH═CH— group.

Schueler (388) found *trans*-4,4′-dihydroxyazobenzene active in the rat subcutaneously at 10–15 mg.; it was reported active at a much lower dosage intravaginally. The author used these results in support of his theory, previously mentioned. Druckrey, Danneberg, and Schmahl (110) and Urushibara and Takahashi (524) confirmed the activity of the compound; the latter found 80 per cent response in mice subcutaneously at 1 mg. The low activity is probably due to the deviation from optimum configuration. This conclusion applies to the series of azomethines prepared by Keasling and Schueler (228).

The data relating to the variation of the aliphatic portion of diethylstilbestrol and hexestrol are collected in table 14.

D. VARIATION OF THE ALIPHATIC PORTION AND OF AROMATIC SUBSTITUTION

Removal of the hydroxyl groups and simultaneous variation of the alkyl groups of the diethylstilbestrol molecule does not abolish estrogenic activity though it greatly reduces it. The activity falls off with increasing size of the alkyl groups (78), but even α-amyl-α′-(1-naphthyl)stilbene (CXXII) is active at 2.0 mg. and indeed is more active than α,α′-dipropyllstilbene (CXXIII). Bibenzyl is incompletely active at 100 mg. (78), and comparison with 4,4′-dihydroxybibenzyl, previously mentioned, indicates that the former is hydroxylated *in vivo*. 4,α-Diethylstilbene (CXXIV) was found inactive (78); presumably the 4-ethyl



$C_6H_5C(C_5H_{11})=CC_6H_5$

CXXII

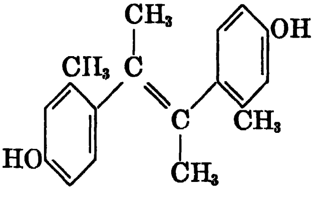
$C_6H_5C(C_3H_7)=C(C_3H_7)C_6H_5$

CXXIII

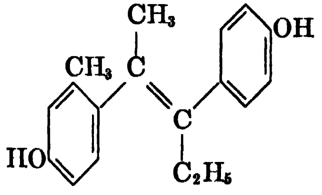
$p\text{-}C_2H_5C_6H_4C(C_2H_5)=CHC_6H_5$

CXXIV

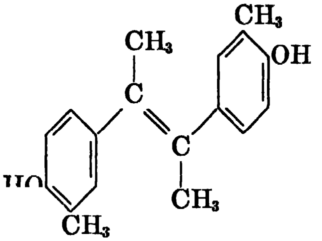
group will prevent hydroxylation biochemically. Hudson and Walton (194) prepared 4,4′-dihydroxy-α,α′,2,2′-tetramethylstilbene by the Dodds synthesis from 2,2′-dimethylanisoin. The intermediate was obtained by the Friedel-Crafts reaction with 2-methyl-4-methoxyphenylacetyl chloride and *m*-methylanisole; the benzoin condensation with 4-methoxy-2-methylbenzaldehyde failed to give the intermediate. The compound presumably has the configuration shown in formula CXXV and is probably quite close to planar. CXXV, with respect to its methyl groups, has little resemblance to the carbon skeleton of the natural estrogens. The compound, perhaps surprisingly, is highly active, being 1.5 times as active as diethylstilbestrol when given subcutaneously to rats (37). The high activity of the saturated analog confirms the earlier report of Bretschneider, Bretschneider, and Ajtai (35). Orally CXXV has about six times the activity of diethylstilbestrol and is more active than the latter when given in the diet. It appears that the superior activity of CXXV lies in its more appropriate physical properties, such as solubility but, as indicated previously, the *o*-methyl groups may be useful in adsorption. The diacetate of CXXV is also highly active (404). α′-Ethyl-4,4′-dihydroxy-α,2-dimethyl-α′-ethyl stilbene (CXXVI) (194) is also more active than diethylstilbestrol both orally and subcutaneously. The hexestrol analogs of these compounds have been made (194, 534, 535). 4,4′-Dihydroxy-α,α′,3′-tetramethylstilbene (CXXVII) with the methyl groups in the meta positions has decreased activity (404), being only half as active as diethylstilbestrol. It was prepared by the condensation of *o*-cresol and biacetyl in 70 per cent sulfuric acid. Attempts to extend the reaction to *m*- or *p*-cresol gave coumarano-coumarane type ethers; *p*-cresol yielded a 2,3,5,5′-tetramethylcoumarano-3′,2,2,3-coumaran, m.p. 196–197°C. (CXXVIII). The same product was obtained by attempted rearrangement of either form of the pinacol from 2-acetyl-4-methylphenol. Oki (322) prepared 2,2′-dichloro-4,4′-dimethoxy-α,α′-dimethylstilbene (CXXIX) and the 2,2′-dibromo and 2,2′-diiodo analogs. Al-



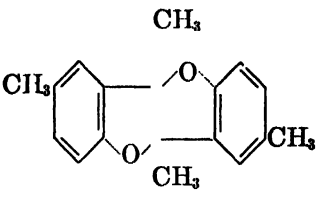
CXXV



CXXVI



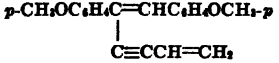
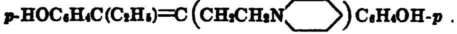
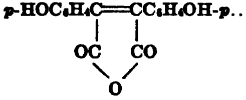
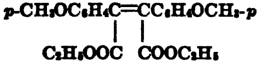
CXXVII



CXXVIII

TABLE 14

Diethylstilbestrol, hexestrol, and dienestrol analogs with variation of the aliphatic portion

Compound	Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
A. Diethylstilbestrol analogs			
	°C.		
p-$HOC_6H_4CH{=}C(CH_3)C_6H_4OH$-$p$	183–184 (trans form)		(18, 379)
Dimethyl ether	124		(188)
Diethyl ether	103–109		(188)
p-$CH_3OC_6H_4C(CH_3){=}C(CH_3)C_6H_4OCH_3$-$p$	50 (cis form)		(544)
	131 (trans form)		(544)
	140.5–142 (trans form)		(327)
p-$CH_3OC_6H_4C(C_3H_7){=}C(C_3H_7)C_6H_4OCH_3$-$p$	111–113 (trans form)	100*‡	(327)
 p-$CH_3OC_6H_4\underset{\displaystyle C{\equiv}CCH{=}CH_2}{\underset{\vert}{C}}{=}CHC_6H_4OCH_3$-$p$	84		(302)
p-$HOC_6H_4C(CH{=}CH_2){=}C(CH{=}CH_2)C_6H_4OH$-$p$	207–208	0.0004 mg.	(103)
		0.0003 mg. (80%)	(103)
		0.0002 mg. (40%)	(103)
	202–203		(134)
p-$HOC_6H_4C(C_2H_5){=}C[CH_2CH_2N(CH_3)_2]C_6H_4OH$-$p$			(469)
p-$HOC_6H_4C(C_2H_5){=}C[CH_2CH_2N(C_2H_5)_2]C_6H_4OH$-$p$			(469)
p-$HOC_6H_4C(C_2H_5){=}C[CH_2CH_2N(C_4H_9)_2]C_6H_4OH$-$p$			(469)
			(469)
p-$CH_3OC_6H_4C(SCH_3){=}C(SCH_3)C_6H_4OCH_3$-$p$	194–196	10*‡	(325, 522)
p-$HOC_6H_4C(C_2H_5){=}C(OCH_3)C_6H_4OH$-$p$	194–195	10*§	(489)
p-$CH_3OC_6H_4CH{=}C(CN)C_6H_4OCH_3$-$p$	105–107		(41)
			(539)
 p-$HOC_6H_4\underset{\vert}{C}{=}\underset{\vert}{C}C_6H_4OH$-$p$, $OC{-}O{-}CO$	224	Inactive	(173)
Dimethyl ether	171	Inactive	(173)
Diacetate	163	Inactive	(173)
 p-$CH_3OC_6H_4\underset{\displaystyle C_2H_5OOC}{\underset{\vert}{C}}{=}\underset{\displaystyle COOC_2H_5}{\underset{\vert}{C}}C_6H_4OCH_3$-$p$	80		(173)

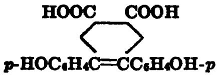
 $p\text{-}HOC_6H_4C{=}CC_6H_4OH\text{-}p$	212–214	10 mg. (inactive)	(103)
$p\text{-}CH_3OC_6H_4CCl{=}CClC_6H_4OCH_3\text{-}p$	163–164	200*‡	(320)
$p\text{-}CH_3OC_6H_4CBr{=}CBrC_6H_4OCH_3\text{-}p$	198	300*‡	(320)
$p\text{-}CH_3OC_6H_4CI{=}CIC_6H_4OCH_3\text{-}p$	173 (d.)	800*‡ (inactive)	(320)
$p\text{-}CH_3OC_6H_4CCl{=}CIC_6H_4OCH_3\text{-}p$	176–177	100*‡	(320)
$p\text{-}CH_3OC_6H_4CBr{=}CIC_6H_4OCH_3\text{-}p$	207 (d.)	>600*‡	(320)
$p\text{-}HOC_6H_4N{=}NC_6H_4OH\text{-}p$		1 mg.*‡ (80%)	(490, 524)
		500*‡ (20%)	(490, 524)
		10–15 mg.	(388)
			(110)
$p\text{-}HOC_6H_4CH{=}NC_6H_4OH\text{-}p$	209	12.5 mg.§	(228)
		25¶	(228)
	208 (polymorphic form)		(228)
	205 (polymorphic form)		(228)
$p\text{-}HOC_6H_4CH{=}NC_6H_4OCH_3\text{-}p$	211	25 mg. (inactive)	(228)
$p\text{-}CH_3OC_6H_4CH{=}NC_6H_4OH\text{-}p$	189	25 mg. (inactive)	(228)
$p\text{-}CH_3OC_6H_4CH{=}NC_6H_4OCH_3\text{-}p$	146	25 mg. (inactive)	(228)
$(p\text{-}HOC_6H_4)_2C{=}C(C_6H_4OH\text{-}p)_2$	—	1 mg. (inactive)	(103)
	B. Hexestrol analogs		
$p\text{-}HOC_6H_4CH_2CH_2C_6H_4OH\text{-}p$		1 mg.* (inactive)	(45)
$p\text{-}HOC_6H_4CH(CH_3)CH(CH_3)C_6H_4OH\text{-}p$	233 (meso form)		(544)
	226–230 (meso form)		(1)
	139 (racemic form)		(544)
Dimethyl ether	136 (meso form)		(544)
	132.5–133 (meso form)		(399)
	88 (racemic form)		(544)
$p\text{-}HOC_6H_4CH(C_2H_5)CH(CH_3)C_6H_4OH\text{-}p$	186–187		(497, 498, 499)
$p\text{-}HOC_6H_4C(CH_3)_2CH(C_2H_5)C_6H_4OH\text{-}p$	186–187	0 001 mg. (ca. 80%)	(103)
$p\text{-}HOC_6H_4CH(C_4H_9)CH_2C_6H_4OH\text{-}p$	74–75		(302)
Dimethyl ether	174–175		(302)
$p\text{-}HOC_6H_4(CH_3)_2C(CH_2)_2C_6H_4OH\text{-}p$	210–212	10 mg	(190)
$p\text{-}HOC_6H_4CH(C_2H_5)CH(C_3H_7)C_6H_4OH\text{-}p$	170–173		(497, 498, 499)
$p\text{-}HOC_6H_4C(CH_3)(C_2H_5)CH(C_2H_5)C_6H_4OH\text{-}p$	182–184	0.0005 mg.	(103)
		0.0003 mg. (ca. 50%)	(103)
$p\text{-}HOC_6H_4CH(C_3H_7)CH(C_3H_7)C_6H_4OH\text{-}p$	166–167 (meso form)		(403)
	168 (meso form)		(48)
			(233)
	Oil (racemic form)		(48)

TABLE 14—*Continued*

Compound	Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B Hexestrol analogs—*Continued*			
	°*C.*		
Dimethyl ether	123 (meso form)		(48)
		1 mg.*	(45)
	Oil (racemic form)		(48)
p-$\mathrm{HOC_6H_4CH(C_2H_5)CH(C_4H_9)C_6H_4OH}$-*p*	135–140		(497, 498, 499)
p-$\mathrm{HOC_6H_4CH(C_4H_9)CH(C_4H_9)C_6H_4OH}$-*p*	167–168 (meso form)		(48)
		0.1 mg *	(45)
	170–171 (meso form)		(403)
p-$\mathrm{HOC_6H_4CH(}$*i*$\mathrm{\text{-}C_4H_9)CH(}$*i*$\mathrm{\text{-}C_4H_9)C_6H_4OH}$-*p*	206–207 (meso form)		(48)
		1 mg.*	(45)
	167–170 (meso form)		(403)
Dimethyl ether	127–128		(48)
		1 mg * (inactive)	(45)
p-$\mathrm{HOC_6H_4CH(C_5H_{11})CH(C_5H_{11})C_6H_4OH}$-*p*	145–146 (meso form)		(403)
p-$\mathrm{HOC_6H_4CH(}$*i*$\mathrm{\text{-}C_5H_{11})CH(}$*i*$\mathrm{\text{-}C_5H_{11})C_6H_4OH}$-*p*	119–120 (meso form)		(48)
(*p*-$\mathrm{HOC_6H_4)_2CHCH(C_6H_4OH}$-*p*$)_2$	299–300	100 (inactive)	(560)
Tetramethyl ether	187.5	100 (inactive)	(560)
Tetraethyl ether	159		(560)
Tetraacetate	283	100 (inactive)	(560)
p-$\mathrm{CH_3OC_6H_4CH(C_2H_5)CH(SCH_3)C_6H_4OCH_3}$-*p*	152.5–154.5	100*‡	(324, 522)
p-$\mathrm{HOC_6H_4CH(SCH_3)CH(SCH_3)C_6H_4OH}$-*p*	193.5–195	40*‡	(326, 521)
		20*‡(67%)	(326, 521)
p-$\mathrm{CH_3OC_6H_4CH(SCH_3)CH(OCH_3)C_6H_4OCH_3}$-*p*	190–191	100*‡	(324, 522)
p-$\mathrm{HOC_6H_4CH(C_2H_5)CH(OCH_3)C_6H_4OH}$-*p*	187–188	1*‡	(485)
Dimethyl ether	120–121	10*‡	(485)
p-$\mathrm{HOC_6H_4CH(OCH_3)CH(OCH_3)C_6H_4OH}$-*p*	220–222 (meso form)	0.5*‡	(487, 523)
p-$\mathrm{HOC_6H_4CH(OC_2H_5)CH(OC_2H_5)C_6H_4OH}$-*p*	212.5–214.5	10*‡	(487, 523)
p-$\mathrm{HOC_6H_4CH(C_2H_5)N(C_2H_5)C_6H_4OH}$-*p*	100.5		(315, 316)
Dimethyl ether	64.5–65	60*‡ (incompletely active)	(315, 316)
p-$\mathrm{HOC_6H_4CH(C_2H_5)CH(NHCH_3)C_6H_4OH}$-*p*	120	30*‡	(486)
Dimethyl ether	91.5–93	100*‡	(486)
		50*‡(60%)	(486)
p-$\mathrm{CH_3OC_6H_4CH(C_2H_5)CH(COOH)C_6H_4OCH_3}$-*p*	181–183		(41)
	177.5–179		(202)
	163–164.5 (isomeric form)		(202)

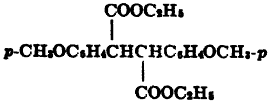
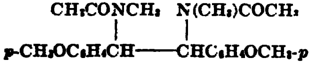
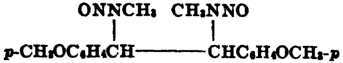
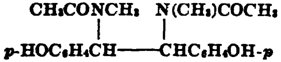
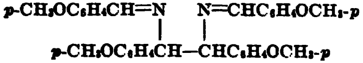
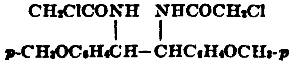
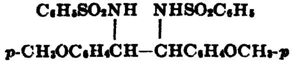
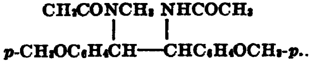
p-$HOC_6H_4C(CH_3)(COOH)CH(C_2H_5)C_6H_4OH$-$p$	225 (d.)	20	(202, 203)
Dimethyl ether	181–182.5	500 (inactive)	(202, 203)
 $p\text{-}CH_3OC_6H_4\overset{COOC_2H_5}{CH}\underset{COOC_2H_5}{CH}C_6H_4OCH_3\text{-}p$	145 (meso form)		(173)
	143–144 (meso form)		(189)
p-$CH_3OC_6H_4CH(COOH)CH(COOH)C_6H_4OCH_3$-$p$	220 (impure racemic form)		(173, 189)
	214–215 (racemic form)		(189)
	272–273 (meso form)		(189)
p-$HOC_6H_4CH(COOH)CH(COOH)C_6H_4OH$-$p$	230 (impure racemic form)	Active	(173, 189)
	225–226 (d.) (racemic form)	5 mg.** (inactive)	(189)
	284 (d.) (meso form)	10 mg.** (inactive)	(189)
p-$HOC_6H_4CH(CH_2COOH)CH(CH_2COOH)C_6H_4OH$-$p$	318–320		(103)
		Inactive	(189)
p-$HOC_6H_4CH(CH_2CH_2OH)CH(CH_2CH_2OH)C_6H_4OH$-$p$	247–249 (meso form)	10 mg. (inactive)	(103)
	178 (racemic form)	10 mg. (inactive)	(103)
p-$CH_3COOC_6H_4CH(CH_2NO_2)CH(CH_2NO_2)C_6H_4OCOCH_3$-$p$	243–245		(34, 36)
	147–150 (isomeric form)		(34, 36)
p-$CH_3OC_6H_4CH(NHCH_3)CH(NHCH_3)C_6H_4OCH_3$-$p$	145		(307)
	134	1000*‡	(488)
Hydrochloride	273 (d.)	100 (inactive)	(307)
Hydroiodide	260 (d.)		(307)
 $p\text{-}CH_3OC_6H_4\overset{CH_3CONCH_3}{CH}\text{—}\overset{N(CH_3)COCH_3}{CH}C_6H_4OCH_3\text{-}p$	218		(307)
 $p\text{-}CH_3OC_6H_4\overset{ONNCH_3}{CH}\text{—}\overset{CH_3NNO}{CH}C_6H_4OCH_3\text{-}p$	238 (d.)		(307)
p-$HOC_6H_4CH(NHCH_3)CH(NHCH_3)C_6H_4OH$-$p$	183 (d.)		(307)
	175		(488)
Hydrochloride	269 (d.)	100 (inactive)	(307)
Hydrobromide	272 (d.)		(307)
Hydroiodide	278 (d.)		(307)
 $p\text{-}HOC_6H_4\overset{CH_3CONCH_3}{CH}\text{—}\overset{N(CH_3)COCH_3}{CH}C_6H_4OH\text{-}p$	331 (d.)		(307)
Diacetate	257		(307)
 $\overset{p\text{-}CH_3OC_6H_4CH=N\quad N=CHC_6H_4OCH_3\text{-}p}{p\text{-}CH_3OC_6H_4CH\text{—}CHC_6H_4OCH_3\text{-}p}$	180		(307)

TABLE 14—*Continued*

Compound	Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Hexestrol analogs—*Continued*			
	°C.		
Methiodide	230 (d.)		(307)
 $p\text{-}CH_3OC_6H_4\overset{CH_2ClCONH}{\overset{\vert}{C}H}-\overset{NHCOCH_2Cl}{\overset{\vert}{C}H}C_6H_4OCH_3\text{-}p$	286 (d.)		(307)
 $p\text{-}CH_3OC_6H_4\overset{C_6H_5SO_2NH}{\overset{\vert}{C}H}-\overset{NHSO_2C_6H_5}{\overset{\vert}{C}H}C_6H_4OCH_3\text{-}p$	280 (d.)		(307)
$p\text{-}HOC_6H_4CH(NH_2)CH(NH_2)C_6H_4OH\text{-}p$	205 (d.)		(307)
Hydrochloride	306 (d.)		(307)
Hydrobromide	323 (d.)		(307)
Hydroiodide	301 (d.)		(307)
$p\text{-}CH_3COOC_6H_4CH(NHCOCH_3)CH(NHCOCH_3)C_6H_4OCOCH_3\text{-}p$	350 (d.)		(307)
$p\text{-}CH_3OC_6H_4CH(NHCH_3)CH(NH_2)C_6H_4OCH_3\text{-}p$	94		(307)
 $p\text{-}CH_3OC_6H_4\overset{CH_3CONCH_3}{\overset{\vert}{C}H}-\overset{NHCOCH_3}{\overset{\vert}{C}H}C_6H_4OCH_3\text{-}p$	250		(307)
$p\text{-}HOC_6H_4CH(NHCH_3)CH(NH_2)C_6H_4OH\text{-}p$	—		(307)
Hydroiodide	259 (d.)		(307)
$p\text{-}CH_3OC_6H_4CH(C_2H_5)CH(CN)C_6H_4OCH_3\text{-}p$	131–133.5	1 mg.	(539)
		0.1 mg. (inactive)	(539)
	130–131		(41, 133)
	Oil (isomeric form)		(41, 539)
$p\text{-}HOC_6H_4CH(C_2H_5)CH(CH_2CN)C_6H_4OH\text{-}p$	—	Active	(475)
$p\text{-}CH_3OC_6H_4CH(C_2H_5)CH(COCH_3)C_6H_4OCH_3\text{-}p$	139–142	0.01 mg.	(539)
		0.001 mg. (inactive)	(539)
	142–143		(41)
	99–101 (isomeric form)	10 mg.	(539)
		1 mg. (inactive)	(539)
	103–104 (isomeric form)		(41)
$p\text{-}HOC_6H_4CH(C_2H_5)CH(COCH_3)C_6H_4OH\text{-}p$	218–220	Active	(41)
	Oil (isomeric form)		(41)
Diacetate	143–144		(41)
Diacetate (isomeric form)	103–104		(41)
$p\text{-}CH_3OC_6H_4CH(C_2H_5)CH(CHOHCH_3)C_6H_4OCH_3\text{-}p$	—	0.1 mg.	(539)
		0.01 mg. (inactive)	(539)

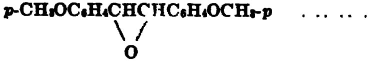
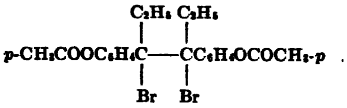
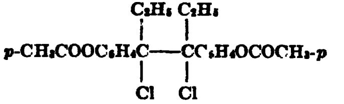
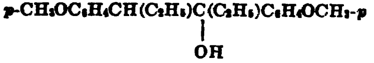
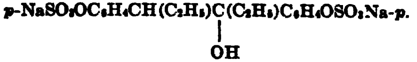
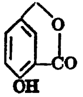
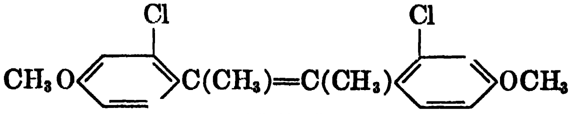
p-$CH_3OC_6H_4CHOHCOC_6H_4OCH_3$-$p$	113	1000 (inactive)	(164)
		100	(63)
p-$CH_3OC_6H_4CHClCOC_6H_4OCH_3$-$p$	81	100	(164)
p-$CH_3OC_6H_4CHBrCOC_6H_4OCH_3$-$p$	104	1000 (inactive)	(164)
 $p\text{-}CH_3OC_6H_4\underset{\diagdown O \diagup}{CHCH}C_6H_4OCH_3\text{-}p$	142	1000 (inactive)	(164)
p-$CH_3OC_6H_4COCOC_6H_4OCH_3$-$p$	133	100 (partial response)	(164)
p-$CH_3OC_6H_4CHOHCHOHC_6H_4OCH_3$-$p$	174	100 (partial response)	(164)
p-$CH_3OC_6H_4CHBrCHBrC_6H_4OCH_3$-$p$	179 (d.)	100 (inactive)	(164)
p-$CH_3OC_6H_4CHClCHClC_6H_4OCH_3$-$p$	184 (d.)	100 (inactive)	(164)
p-$HOC_6H_4COCOC_6H_4OH$-p	235	100 (inactive)	(164)
p-$HOC_6H_4CHOHCHOHC_6H_4OH$-p	222	100 (inactive)	(164)
 $p\text{-}CH_3COOC_6H_4\overset{C_2H_5}{\underset{Br}{C}}-\overset{C_2H_5}{\underset{Br}{C}}C_6H_4OCOCH_3\text{-}p$	156 (d.)	25	(164)
		10 (partial response)	(164)
		1 (inactive)	(164)
	156–156.5 (d.)		(510, 511, 512, 513)
 $p\text{-}CH_3COOC_6H_4\overset{C_2H_5}{\underset{Cl}{C}}-\overset{C_2H_5}{\underset{Cl}{C}}C_6H_4OCOCH_3\text{-}p$	156 (d.)	25	(164)
		10 (partial response)	(164)
p-$NaSO_3OC_6H_4COCHOHC_6H_4OSO_3Na$-$p$			(63)
p-$CH_3OC_6H_4COCH_2C_6H_4OCH_3$-$p$		100	(63)
p-$NaSO_3OC_6H_4COCH_2C_6H_4OSO_3Na$-$p$			(63)
p-$CH_3OC_6H_4CH(C_2H_5)COC_6H_4OCH_3$-$p$		10	(63)
p-$NaSO_3OC_6H_4CH(C_2H_5)COC_6H_4OSO_3Na$-$p$			(63)
 $p\text{-}CH_3OC_6H_4CH(C_2H_5)\underset{OH}{C}(C_2H_5)C_6H_4OCH_3\text{-}p$		10	(63)
 $p\text{-}NaSO_3OC_6H_4CH(C_2H_5)\underset{OH}{C}(C_2H_5)C_6H_4OSO_3Na\text{-}p$			(63)
p-$HOC_6H_4SC_6H_4OH$-p		100 mg.	(65)
		50 mg. (60%)	(65)
		25 mg. (inactive)	(65)

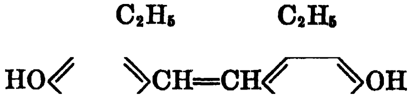
TABLE 14—*Concluded*

Compound	Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise)· Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Hexestrol analogs—*Continued*			
	°C.		
p-$HOC_6H_4SOC_6H_4OH$-p . . .		Inactive	(65)
p-$HOC_6H_4SO_2C_6H_4OH$-p			
p-$CH_3OC_6H_4SC_6H_4OCH_3$-p		Inactive	(65)
p-$CH_3OC_6H_4CH(C_2H_5)SCH(C_2H_5)C_6H_4OCH_3$-$p$		100 mg.	(65)
		50 mg. (50%)	(65)
		25 mg. (inactive)	(65)
p-$HOC_6H_4SSC_6H_4OH$-p . .		Inactive	(65)
p-$HOC_6H_4SC_6H_4OH$-p		Inactive	(65)
			

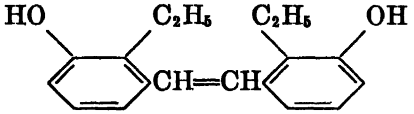
* In mice.
† Orally.
‡ Administered in two portions.
§ Minimal lethal dose.
‖ Administered in five portions.
¶ Administered intravaginally in five portions.
** Administered in aqueous solution.



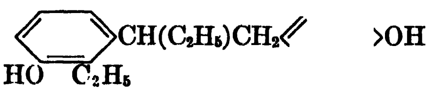
CXXIX



CXXX



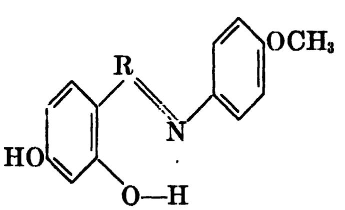
CXXXI



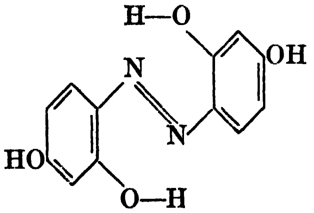
CXXXII

though they resemble CXXV they were much less active. Richtzenhain (352) found 2,2′-diethyl-4,4′-dihydroxystilbene (CXXX) and its dihydro derivative to have only low activity, confirming the result of Linnell and Shaikmahahmud (264). Surprisingly, with the hydroxyl groups in the meta positions the diethylstilbestrol analog (CXXXI) and the hexestrol analog are fairly active, the former giving 87 per cent response at 10 micrograms. After other attempts had failed, CXXXI was obtained by converting 2-ethyl-3-hydroxybenzaldehyde to the thioaldehyde and treating with copper bronze; 2-ethyl-3-methoxybenzaldehyde could not be used, since the final ether could not be demethylated. Hydrogenation of this ether gave the hexestrol analog, which could be demethylated (353). 3-(2-Ethyl-3-hydroxyphenyl)-4-(*p*-hydroxyphenyl)butane (CXXXII) (353) was successfully obtained only by a Friedel–Crafts reaction with 2-ethyl-3-methoxyphenylacetyl chloride and anisole, followed by ethylation of the ketone with sodium ethoxide and ethyl iodide and then by Wolff–Kishner reduction; it was active at 10 micrograms. Neher and Miescher (303) replaced one hydroxyl group of diethylstilbestrol by a carboxyl group and varied the aliphatic portion. 4′-Carboxy-4-hydroxy-α,α′-dipropylstilbene was active at 700–1000 micrograms; the methyl ester of 4′-carboxy-4-hydroxy-α,α′-dimethylstilbene was active at 1 mg., but the free acid was not. This latter result appears to illustrate the idea that a solubilizing carboxyl group tends to aid elimination or a similar process and, depending on the rest of the molecule, may result in inactivity. α′-Carboxy-3-hydroxystilbene, α′-carboxy-3,4′-dihydroxystilbene, and their dihydro compound were inactive at 5 mg. (294).

Nomura (317) prepared a series of azomethines (CXXXIII). The 2-hydroxyl



CXXXIII



CXXXIV

group was introduced in the expectation that intramolecular hydrogen bonding would introduce some rigidity into the molecule, as suggested by Schueler (388). The peak of activity occurred with R = ethyl. Similar compounds were prepared by Keasling and Schueler (228). Takahashi (490) also introduced hydroxyl groups into 4,4′-dihydroxyazobenzene for the purpose of increasing rigidity; the 2,2′,4,4′-tetrahydroxyazobenzene (CXXXIV) was more active than the parent compound. It is difficult to decide whether rigidity in these compounds is responsible for their increased estrogenic activity, since rigidity might be expected to be important only when it affects the relative orientation of the hydrogen-bonding groups. Analogs of diethylstilbestrol, hexestrol, and dienestrol with variation of the aliphatic portion and of aromatic substitution are collected in table 15.

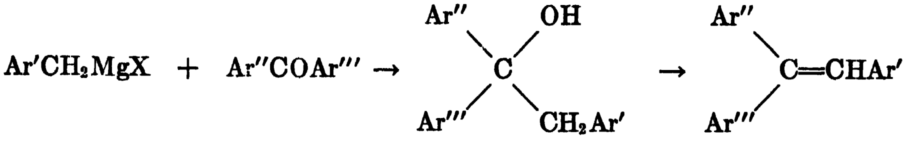
E. TRIPHENYLETHYLENE AND ITS ANALOGS

The discovery of the estrogenic activity of 1,1,2-triphenylethylene and that of certain of its analogs, together with the apparent structural differences in this series compared with diethylstilbestrol, has led to extensive investigation of this class of compounds. Members of the group such as 1,1-bis(*p*-ethoxyphenyl)-2-phenyl-2-bromoethylene (DBE) have been used clinically. Triphenylethylene and its analogs contain the *cis*- and *trans*-stilbene systems and are best considered as variants of diethylstilbestrol.

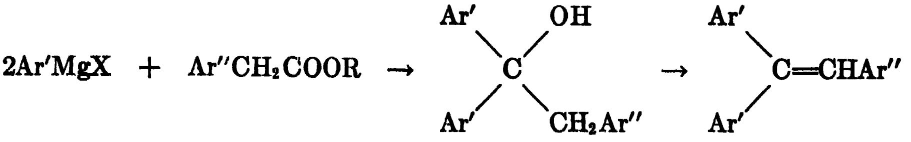
1. Syntheses

Three principal routes have been used for the preparation of estrogenic or potentially estrogenic triphenylethylenes.

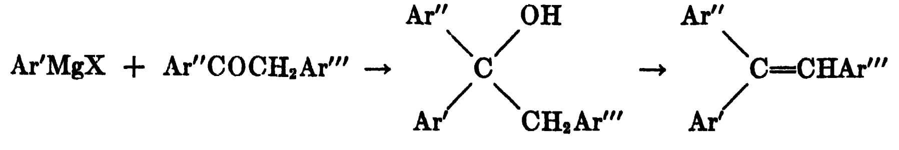
(*a*) From a benzylmagnesium halide and a dialkyl ketone:



(*b*) From an arylmagnesium halide and an arylacetic ester:



(*c*) From an arylmagnesium halide and a desoxybenzoin:



Synthesis (c) provides two routes to the same intermediary carbinol by interchanging Ar′ and Ar″ in the starting materials. The usefulness of the various syntheses depends on the particular triphenylethylene being prepared. Method (a) is not applicable to *p*-alkoxybenzylmagnesium halides, and in all the methods best results are obtained by the use of an excess of the Grignard reagent. In methods (a) and (c) two molecular proportions of the Grignard reagent are used, while in method (b) it is preferable to use three molecular proportions (59). A wide variety of methods has been found useful for the dehydration step; some tertiary carbinol intermediates undergo dehydration spontaneously (44) or on distillation at low pressures (303). The following chemical methods have been used: treatment with iodine in xylene (303); distillation with dilute sulfuric acid (480); refluxing in acetic acid containing acetyl chloride or a trace of sulfuric acid (480); heating with phosphoric acid (396); heating with 100 per cent formic acid (362); heating with a mixture of acetic and hydrobromic acids (477); heating with *p*-toluenesulfonic acid at low pressures (397).

The 2-chloro and 2-bromo derivatives of triphenylethylenes are an important group of estrogens and have been obtained from the corresponding ethylene or directly from the corresponding intermediate carbinol for the ethylene. Treatment with bromine in carbon disulfide (44) or in carbon tetrachloride, acetic acid, nitrobenzene, or chlorobenzene has been used to obtain the 2-bromo compound. A 2–5 per cent excess of halogen is used (15). The 2-chloro compounds may be similarly obtained or by using sulfuryl chloride in the presence of benzoyl peroxide (477). In the second method the carbinol intermediate may be converted to the halogen compound directly by means of a solution of chlorine or bromine in acetic acid or chloroform (59); water is eliminated in this reaction. The method is valuable for its directness and also in that the carbinols are more easily handled than the ethylenes.

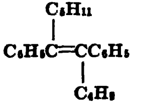
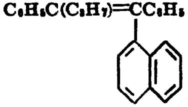
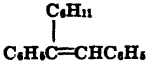
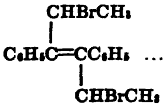
2. Estrogenic activity

The triphenylethylenes, like diethylstilbestrol, hexestrol, and dienestrol, are active by mouth. However, they are distinguished from the latter estrogens in that many of them have the useful property of prolonged action. Only the more important triphenylethylenes, together with some general considerations, will be mentioned here.

The estrogenic activity of triphenylethylene, the parent of the series, was reported almost simultaneously but independently by Robson and Schönberg (364) and by Dodds, Fitzgerald, and Lawson (99). The quite early variations of the parent structure produced some of the most active compounds of the series (457). Triphenylethylene and its 2-chloro and 2-bromo derivatives—provided dosages well above threshold are used—combine sufficiency of estrogenic activity with duration of action, and this characteristic has resulted in clinical interest in this series. However, the introduction of *p* hydroxyl groups into the aromatic rings removes their property of prolongation of action (483), and it appears that the property is associated with the necessity of *in vivo* hydroxylation. However, their storage in body fat (361) and their low solubility in body fluids are probably important additional factors connected with prolonged action. As previously discussed in connection with the stilbene estrogens, optimum physicochemical

TABLE 15

Analogs of diethystilbestrol, hexestrol, and dienestrol with variation of the aliphatic portion and aromatic substitution

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms. Unless Indicated Otherwise	References
	A. Diethylstilbestrol analogs		
	°C.		
$C_6H_5C(C_2H_5)=C(C_3H_7)C_6H_5$		0 1 mg.*	(78)
$C_6H_5CH(C_2H_5)=C(CH_2CH=CH_2)C_6H_5$		0 5 mg.*	(78)
$C_6H_5C(C_2H_5)=C(i\text{-}C_5H_{11})C_6H_5$		0.5 mg.*	(78)
$C_6H_5C(C_2H_5)=C(C_5H_{11})C_6H_5$		2.0 mg.*	(78)
$C_6H_5C(C_3H_7)=C(C_2H_7)C_6H_5$		5.0 mg.*	(78)
$C_6H_5C(C_4H_9)=C(C_2H_7)C_6H_5$		20 mg.*	(78)
 $C_6H_5C(C_5H_{11})=CC_6H_5(C_4H_9)$		20 mg.*	(78)
 $C_6H_5C(C_3H_7)=CC_6H_5$		2 mg.*	(78)
 $C_6H_5C(C_6H_{11})=CHC_6H_5$	208-210/18 mm. (b.p.)		(44)
 $C_6H_5C(CHBrCH_3)=CC_6H_5(CHBrCH_3)$	182 (d.)	1 mg. (50%)	(103)
$C_6H_5CH=CHC_6H_4OCH_2CH_2N(C_2H_5)_2\text{-}p$	74		(277)
$C_6H_5C(CH_3)=C(CH_3)C_6H_4OCH_2CH_2N(C_2H_5)_2\text{-}p$	235-238/9.7 mm. (b.p.)		(277)
$C_6H_5C(i\text{-}C_3H_7)=C(i\text{-}C_3H_7)C_6H_4OCH_2CH_2N(C_2H_5)_2$	38		(277)

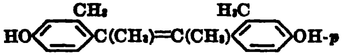
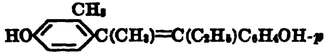
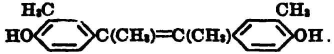
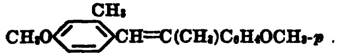
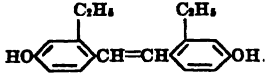
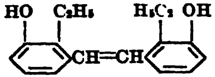
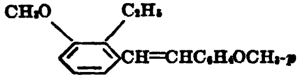
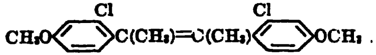
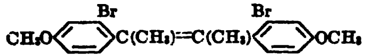
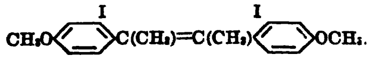
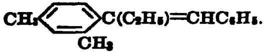
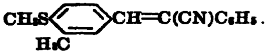
p-$CH_3OC_6H_4C(CH_3)=C(CH_3)C_6H_4OCH_3$-$p$	141.5–143	100*‡	(322)
	208–210		(194, 534)
		1.5§	(37)
	214	6.2†§	(37)
Diacetate	116–117	10,000 (I.U./mg.)	(404, 405)
		5000 (I.U./mg.)	(404, 405)
	153–154		(534)
		1.2§	(37)
		4.8†§	(37)
	197–198	Half the activity of diethylstilbestrol	(404)
	96–97 (trans form)		(534)
	Oil (cis form)		(534)
	151	1 mg.*	(352)
	191–192	10* (87%)	(353)
	81		(353)
	112–113 (trans form)	200*‡	(322)
	117.5–119.5 (trans form)	200*‡	(322)
	159–160 (trans form)	500*‡ (75%)	(322)

TABLE 15—*Continued*

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
A. Diethylstilbestrol analogs—*Continued*			
	°*C*		
m-$HOC_6H_4CH{=}C(COOH)C_6H_5$	187–188	5 mg.* (inactive)	(294)
m-$HOC_6H_4CH{=}C(COOH)C_6H_4OH$-*p*	230 (d.)	5 mg.* (inactive)	(294)
p-$HOC_6H_4CH{=}CHC_6H_4COOH$-*p*	277–278	1 mg. (inactive)	(303)
	300–302 (isomeric form)		(303)
p-$HOC_6H_4C(CH_3){=}C(CH_3)C_6H_4COOH$-*p*	231–234	1 mg. (inactive)	(303)
Methyl ester	160–162	1 mg.	(303)
		0.5 mg. (inactive)	(303)
p-$HOC_6H_4CH{=}C(C_2H_5)C_6H_4COOH$-*p*	144–146 (from benzene)	1 mg. (inactive)	(303)
	128–133 (from aqueous methanol)		(303)
p-$HOC_6H_4C(C_2H_5){=}CHC_6H_4COOH$-*p*	144–149	1 mg. (inactive)	(303)
	191–196 (polymorphic form)		(303)
p-$HOC_6H_4C(C_3H_7){=}C(C_3H_7)C_6H_4COOH$-*p*	176–178	1000	(303)
		700 (40%)	(303)
p-$H_2NC_6H_4C(CH_3){=}C(CH_3)C_6H_4NH_2$-*p*	145–146		(8, 9)
p-$CH_3SC_6H_4C(CH_3){=}C(CH_3)C_6H_4SCH_3$-*p*	132.5–133.5	300*‡ (50%)	(321)
p-$CH_3SC_6H_4C(C_3H_7){=}C(C_3H_7)C_6H_4SCH_3$-*p*	99–99.5	200*‡ (incomplete)	(321)
p-$CH_3C_6H_4C(C_2H_5){=}CHC_6H_5$	203–204/35 mm. (b.p.)		(44)
p-$CH_3C_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_5$	197–198/29 mm. (b.p.)		(44)
p-$CH_3C_6H_4C(C_2H_5){=}C(C_3H_7)C_6H_5$	202/28 mm. (b.p.)		(44)
p-$CH_3C_6H_4C(C_2H_5){=}C(C_4H_9)C_6H_5$	207–208/25 mm. (b.p.)		(44)
p-$C_2H_5C_6H_4C(C_2H_5){=}CHC_6H_5$	210/30 mm. (b.p.)		(44)
		1 mg.* (inactive)	(78)
p-$(CH_3)_3CC_6H_4C(C_2H_5){=}CHC_6H_5$	205–206/20 mm. (b.p.)		(44)
 $CH_3C_6H_3(CH_3)C(C_2H_5){=}CHC_6H_5$	198–199/25 mm. (b.p.)		(44)
p-$CH_3SC_6H_4CH{=}C(CN)C_6H_5$	96		(49)
p-$CH_3SC_6H_4CH{=}C(CN)C_6H_4CH_3$-*p*	113		(49)
p-$CH_3SC_6H_4CH{=}C(CN)C_6H_4F$-*p*	117		(49)
p-$CH_3SC_6H_4CH{=}C(CN)C_6H_4Cl$-*p*	100		(49)
p-$CH_3SC_6H_4CH{=}C(CN)C_6H_4Br$-*p*	131		(49)
p-$CH_3SC_6H_4CH{=}C(CN)C_6H_4I$-*p*	135		(49)
 $CH_3SC_6H_3(CH_3)CH{=}C(CN)C_6H_5$	99		(49)

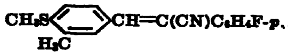
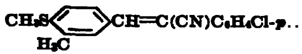
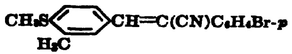
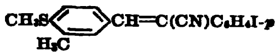
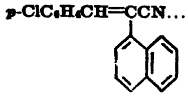
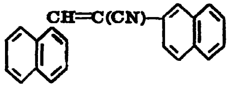
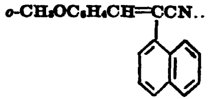
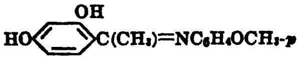
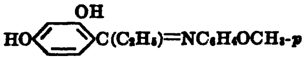
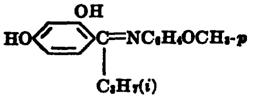
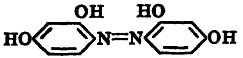
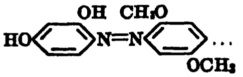
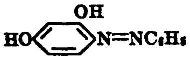
	123		(49)
	134		(49)
	132		(49)
	152		(49)
p-$CH_3OC_6H_4CH{=}C(CN)C_6H_4CH_3$-$p$		10 mg.* (inactive)	(45)
o-$CH_3OC_6H_4CH{=}C(CN)C_6H_4CH_3$-$p$		10 mg.* (inactive)	(45)
p-$ClC_6H_4CH{=}C(CN)C_6H_5$		10 mg.* (inactive)	(45)
		10 mg.* (inactive)	(45)
p-$(CH_3)_2NC_6H_4CH{=}C(CN)C_6H_5$		10 mg.* (inactive)	(45)
p-$(CH_3)_2NC_6H_4CH{=}C(CN)C_6H_4CH_3$-$p$		10 mg.* (inactive)	(45)
o-$CH_3OC_6H_4CH{=}C(CN)C_6H_5$		10 mg.* (inactive)	(45)
p-$ClC_6H_4CH{=}C(CN)C_6H_4CH_3$-$p$		1 mg.* (inactive) 5 mg.* (toxic)	(45) (45)
		1 mg.* (inactive)	(45)
		1 mg.* (inactive)	(45)
p-$(i$-$C_3H_7)C_6H_4CH{=}C(CN)C_6H_4CH_3$-$p$		1 mg.* (inactive)	(45)
p-$[p$-$CH_3OC_6H_4]C_6H_4C(C_2H_5){=}CHC_6H_5$		1 mg.* (inactive)	(45)
$C_6H_5CH{=}NC_6H_5$	54	25 mg. (inactive)	(228)
$C_6H_5CH{=}NC_6H_4CH_3$-p	36	25 mg. (inactive)	(228)
$C_6H_5CH{=}NC_6H_4OCH_3$-p	70	25 mg. (inactive)	(228)
$C_6H_5CH{=}NC_6H_4OH$-p	185	25 mg. (inactive)	(228)
p-$CH_3C_6H_4CH{=}NC_6H_5$	41	25 mg. (inactive)	(228)

TABLE 15–*Continued*

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	Reference
A. Diethylstilbestrol Analogs—*Continued*			
	°C.		
p-$CH_3C_6H_4CH{=}NC_6H_4CH_3$-p	93	25 mg. (inactive)	(228)
p-$CH_3C_6H_4CH{=}NC_6H_4OCH_3$-p	87	25 mg. (inactive)	(228)
p-$CH_3C_6H_4CH{=}NC_6H_4OH$-p	200	25 mg. (inactive)	(228)
p-$CH_3OC_6H_4CH{=}NC_6H_5$	57	25 mg. (inactive)	(228)
p-$CH_3OC_6H_4CH{=}NC_6H_4CH_3$-p	94	25 mg. (inactive)	(228)
p-$HOC_6H_4CH{=}NC_6H_5$	194	25 mg. (inactive)	(228)
p-$HOC_6H_4CH{=}NC_6H_4CH_3$-p	220	25 mg. (inactive)	(228)
	262 (d.)	1 mg.*‡ (inactive)	(317, 318)
	213 (d.)	1 mg.*‡	(317, 318)
	197 (d.)	1 mg.*‡ (40%)	(317, 318)
		20*‡ 10*‡ (60%)	(490) (490)
		1 mg.*‡ (inactive)	(490)
		500*‡ (40%)	(490)

B. Hexestrol analogs

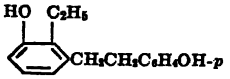
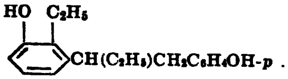
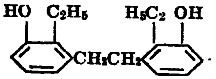
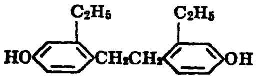
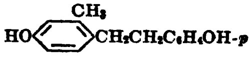
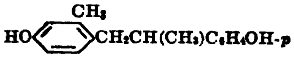
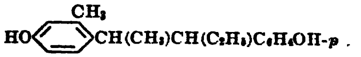
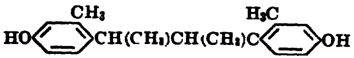
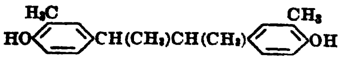
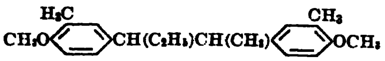
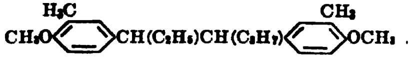
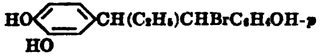
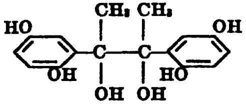
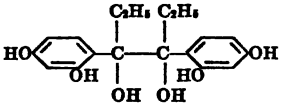
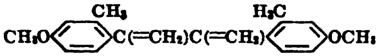
$C_6H_5CH_2CH_2C_6H_5$		100 mg. (incompletely active)	(78)
$C_6H_5CH(C_4H_9)CH(C_4H_9)C_6H_5$	77 (meso form) Oil (racemic form)		(48) (48)
	97–98	0.5 mg.*	(353)
	180/0.3 mm. (b.p.)	10* 5* (75%)	(353) (353)
	154–155	20* (87%) 10* (25%)	(353) (353)
	133	1 mg.*	(352)
	144–145		(534, 535)
	131–133		(534, 535)
	140–141		(534, 535)
	189–190		(194, 534, 535)
	174–174.5 (meso form)		(402, 403)
	195–200/2 mm. (b.p.)		(496)

TABLE 15—*Concluded*

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms Unless Indicated Otherwise	References
B. Hexestrol analogs—*Continued*			
	°*C.*		
	195–205/2 mm. (b.p.)		(496)
	130–133		(497)
	240–244	50 mg. (inactive)	(140)
Hexaacetate	213–215	50 mg. (inactive)	(140)
	233–234 (α-isomer)	50 mg. (23 days)[‖]	(140)
		5 mg. (2.5 days)[‖]	(140)
		2 mg. (inactive)	(140)
	200–201 (β-isomer)	50 mg. (1 day)[‖]	(140)
		25 mg. (1 day)[‖]	(140)
		5 mg. (inactive)	(140)
Hexaacetate	227–230 (α-isomer)	5 mg. (2.5 days)	(140)
m-$HOC_6H_4CH_2CH(COOH)C_6H_5$	75	5 mg.[*] (inactive)	(294)
m-$CH_3OC_6H_4CH_2(COOH)C_6H_4OCH_3$-*p*	104	5 mg.[*] (inactive)	(294)
p-$CH_3OC_6H_4CH(C_2H_5)CH(CN)C_6H_5$	69–71	10 mg. (inactive)	(539)
	118–119 (isomeric form)	10 mg. (inactive)	(539)
p-$CH_3OC_6H_4CH(C_2H_5)CH(COCH_3)C_6H_5$	108–109.5	0.1 mg.	(539)
		0.01 mg. (inactive)	(539)
	63–66 (isomeric form)		(539)
p-$HOC_6H_4C(C_2H_5)(OH)CH(C_2H_5)C_6H_4NH_2$-*p*	181–182	1 mg.[*]	(216)
		0.1 mg.[*] (78%)	(216)
		0.01 mg.[*] (inactive)	(216)

p-$CH_3SC_6H_4CH(C_3H_7)CH(C_3H_7)C_6H_4SCH_3$-$p$	112		(49)
$C_6H_5SC_6H_5$		Inactive	(65)
p-$O_2NC_6H_4SC_6H_4NO_2$-p		Inactive	(65)
p-$H_2NC_6H_4SC_6H_4NH_2$-p	107–108	Inactive	(65)
p-$O_2NC_6H_4CH(C_2H_5)SCH(C_2H_5)C_6H_4OH$-$p$		Inactive	(65)
	C. Dienestrol analogs		
$C_6H_5CH(CH{=}CH_2)CH(CH{=}CH_2)C_6H_5$	87–87.5 (meso form)	1–10 mg. (50%)	(240)
	Oil (racemic form)		(240)
p-$HOC_6H_4C({=}CH_2)C({=}CH_2)C_6H_4OH$-$p$	166–167		(1, 178)
Dimethyl ether	108–109		(404)
	108–108.5		(404)

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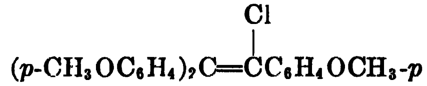
* In mice.
† Orally.
‡ Administered in two portions.
§ Diethylstilbestrol = 1.
‖ Duration of estrus.

properties are apparently essential in the triphenylethylene series. In connection with the concept of proestrogens to be discussed later, Emmens (115) found various triphenylethylenes to be proestrogens. Basford (15) noted that the introduction of *p*-methoxy groups into the 1-phenyl groups of triphenylethylene and its halogen derivatives resulted in estrogens which were more active orally than subcutaneously.

Rothschild and Keys (367) assessed the estrogen tris(*p*-methoxyphenyl)-chloroethylene (CXXXV) (TACE) in the human subject and found that the



$$(p\text{-}CH_3OC_6H_4)_2C{=}\overset{\overset{\displaystyle Cl}{|}}{C}C_6H_4OCH_3\text{-}p$$

CXXXV

minimal effective dose on oral administration for complete cornification of the postmenopausal human female vagina was 24–48 mg., administered as four daily doses of 6–12 mg. each. Administration of the same quantities of this estrogen but on alternate days did not lead to much cornification. This result implies fairly rapid destruction of this estrogen in the body, and it is of interest that Morin, de Clercq, Apelgot, and Daudel (292) showed, using radiobromotriphenylethylene subcutaneously in mice and rabbits, that the substance is rapidly destroyed. The bromine was found to be excreted as inorganic bromide. The ease of destruction of triphenylethylenes, as indicated by these results, may be important when comparing the estrogenic activities of compounds. Rothschild and Keys (367) also showed that with the triphenylethylene TACE in minimal dosage, the duration of estrus was not greatly different from that produced by the stilbene estrogens. However, this estrogen contains potential hydroxyl groups and probably with the exception of massive dosage it is likely that appreciable fat storage is associated with the absence of hydroxyl groups or their equivalents.

Thompson and Werner (504) found TACE more prolonged in action subcutaneously than orally. However, large oral doses in rats did lead to some increased duration of action. The estrogen was in fact found to be stored in body fat, but no such storage was found for diethylstilbestrol or hexestrol; neither did these latter estrogens exhibit prolonged action. As pointed out previously, free hydroxyl groups are unlikely to lead to fat storage, and presumably such storage of TACE at higher dosage is accounted for by the absence of free hydroxyl groups. With monkeys and rats it was found that estrogenic material equivalent in biological activity to more than the administered dose of TACE was eliminated with feces. Dealkylation *in vivo* may account for this. With hexestrol little estrogenic material was excreted. The estrogenic activities found by Thompson and Werner (504) for TACE and the relation to diethylstilbestrol and hexestrol are given in table 16.

3. Structure and estrogenic activity

The extensive investigations in this series make it profitable to consider the effect of structural variation on estrogenic activity along lines similar to those used in discussing diethylstilbestrol, hexestrol, and dienestrol.

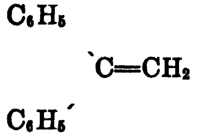
TABLE 16

Estrogenic activities of tris(p-methoxyphenyl)chloroethylene and their relation to diethylstilbestrol and hexestrol

Compound	Dose		Median Duration	
	Subcutaneously	Orally	Subcutaneously	Orally
	mg.	*mg.*	*days*	*days*
Tris(*p*-methoxyphenyl)chloroethylene	1 (18 rat units)	1 (47 rat units)	53	2
		5 (238 rat units)		17
Hexestrol	1 (2857 rat units)	1 (83 rat units)	2	3
		5 (415 rat units)		2
Diethylstilbestrol	1 (2500 rat units)	1 (333 rat units)	3	2
		5 (1666 rat units)		3

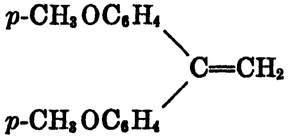
(a) Variation of aromatic substitution

The three phenyl groups in triphenylethylene are essential to higher estrogenic activities; 1,1-diphenylethylene (CXXXVI) (99) is inactive. The related compound 1,1-bis(*p*-methoxyphenyl)ethylene (CXXXVII) (481) is also inactive at 5 mg.



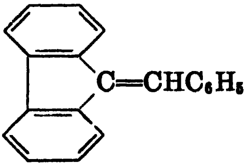
$$(C_6H_5)_2C{=}CH_2$$

CXXXVI



$$(p\text{-}CH_3OC_6H_4)_2C{=}CH_2$$

CXXXVII



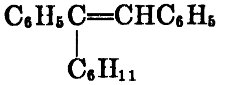
CXXXVIII

Triphenylethylene itself was reported active in mice subcutaneously at 0.1 mg. by Lacassagne, Buu-Hoï, Corre, Lecocq, and Royer (251); 300 micrograms was reported to give 50 per cent response in mice subcutaneously by Emmens (115); Jacques, Courrier, and Pomeau-Delille (209) reported a subcutaneous activity in rats of 10 mg. in a divided dose. These low activities are reminiscent of those of unhydroxylated stilbene derivatives discussed previously and point to the need for hydroxylation of triphenylethylene before it can exhibit estrogenic function. Triphenylethylene contains both the *cis*- and *trans*-stilbene units, and the well-known *cis*-stilbene steric effect will operate. This steric interaction between a 1-phenyl and the 2-phenyl group will result in rotation of the rings. A 1-phenyl group appears to fulfill a steric function similar to that discussed previously for ethyl groups in diethylstilbestrol. Little steric interaction will presumably occur between the 1-phenyl groups, but the one not hindered by the 2-phenyl group should be capable of orientation, giving the *trans*-stilbene unit the staggered configuration of diethylstilbestrol. Triphenylethylene is more active than *trans*-stilbene and has about the same activity as α-ethyl-α'-propylstilbene previously mentioned. Linking of the two 1-phenyl groups as in 9-benzylidenefluorene (CXXXVIII) (144, 209) results in a weak estrogen, probably owing to the inability of the molecule to adopt appropriate configuration. Apparently this is a case where rigidity of the molecule is disadvantageous.

2-Cyclohexyl-1,1-diphenylethylene (CXXXIX) (362) rather surprisingly is active, while 1-cyclohexyl-1,2-diphenylethylene (CXL) is inactive. The activity of

$(C_6H_5)_2C{=}CHC_6H_{11}$

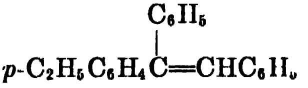
CXXXIX



$C_6H_5\underset{C_6H_{11}}{\underset{|}{C}}{=}CHC_6H_5$

CXL

the former is probably due to its "diphenylmethane" unit, while the latter probably has the cis configuration of aromatic rings (168). 1-(*p*-Ethylphenyl)-1,2-diphenylethylene (CXLI) has low activity (251), suggesting that the rings are trans oriented, since *p*-alkyl groups in the stilbene series abolish activity. 1,1-Bis(4-biphenyl)-2-phenylethylene (CXLII) is inactive (79); here certain blocking of the para positions occurs.



$p\text{-}C_2H_5C_6H_4\overset{C_6H_5}{\overset{|}{C}}{=}CHC_6H_5$

CXLI

$(p\text{-}C_6H_5C_6H_4)_2C{=}CHC_6H_5$

CXLII

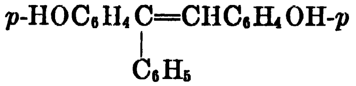
The introduction of a hydroxyl group into the para position of one of the 1-phenyl groups of triphenylethylene considerably enhances the estrogenic activity relative to the parent compound (115). 1,1-Bis(*p*-hydroxyphenyl)-2-phenylethylene (CXLIII) gives 50 per cent response in mice subcutaneously at 8 micrograms. The related compound 1,1-bis(*p*-methoxyphenyl)-2-phenylethane (CXLIV) (45) is active in mice subcutaneously at 2 mg., but its configuration is not definite. 1,2-Bis(*p*-hydroxyphenyl)-1-phenylethylene (CXLV) is also highly active, producing 50 per cent response in mice subcutaneously at 15 micrograms (115). Hydroxyl groups considerably increase the potency of compounds in the triphenylethylene series and in fact are optimum groups for this purpose. However, as indicated previously, they also lead to loss of duration of action.

$(p\text{-}HOC_6H_4)_2C{=}CHC_6H_5$

CXLIII

$(p\text{-}CH_3OC_6H_4)_2CHCH_2C_6H_5$

CXLIV



$p\text{-}HOC_6H_4\underset{C_6H_5}{\underset{|}{C}}{=}CHC_6H_4OH\text{-}p$

CXLV

1,1-Bis(*p*-methylthiophenyl)-2-phenylethylene (CXLVI) (301) and 1,1-bis-(*p*-dimethylaminophenyl)-2-phenylethylene (CXLVII) (78) are inactive. The inactivity of CXLVI is of interest in view of the conflicting reports on the effect of methylthio groups on the activity of the stilbene estrogens mentioned earlier.

$(p\text{-}CH_3SC_6H_4)_2C{=}CHC_6H_5$

CXLVI

$p\text{-}[(CH_3)_2NC_6H_4]_2C{=}CHC_6H_5$

CXLVII

$(p\text{-}CH_3OC_6H_4)_2C{=}CHC_6H_4COOH\text{-}p$

CXLVIII

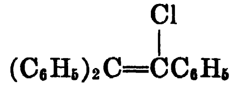
$(p\text{-}CH_3OC_6H_4)_2C{=}CHC_6H_4Cl\text{-}p$

CXLIX

1,1-Bis(*p*-methoxyphenyl)-2-(*p*-carboxyphenyl)ethylene (CXLVIII) is inactive at 1 mg. (303). Some attention has been paid to the introduction of halogen atoms into the triphenylethylene molecule (482); 1,1-bis(*p*-methoxyphenyl)-2-(*p*-chlorophenyl)ethylene (CXLIX) at 1000 micrograms in mice has a median duration of action of 3 days. It appears that the halogen atom, unlike most others, can be replaced *in vivo* by the hydroxyl group.

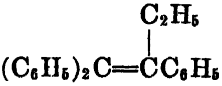
(b) Variation of the aliphatic portion

Shortly after the discovery of the estrogenic activity of triphenylethylene, Robson, Schönberg, and Fahim (365) showed that 2-chloro-1,1,2-triphenylethylene (CL) is rather more potent than the parent substance. Barbier, Rumpf,



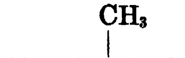
$(C_6H_5)_2C{=}\overset{Cl}{\overset{|}{C}}C_6H_5$

CL



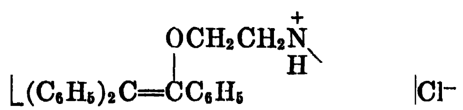
$(C_6H_5)_2C{=}\overset{C_2H_5}{\overset{|}{C}}C_6H_5$

CLI



$(C_6H_5)_2\overset{CH_3}{\overset{|}{C}}COC_6H_5$

CLII



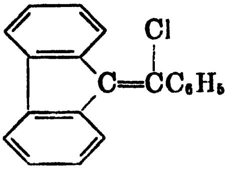
$\left[(C_6H_5)_2C{=}\overset{OCH_2CH_2\overset{+}{N}H}{\overset{|}{C}}C_6H_5\right]Cl^-$

CLIII

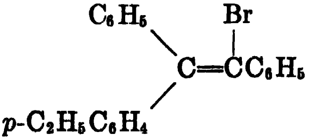
and Roland (14) tested the 2-chloro,2-bromo, and 2-iodo compounds and found that the order of effectiveness for estrogenic potency was chlorine > bromine > iodine. Schueler (388) suggested that the inductive effect of the halogen atoms results in the *p*-hydrogen atoms of the 1-phenyl groups acquiring fractional positive charge and hence some hydrogen-bonding capacity. Clark (73), however, considered that the prolonged action of triphenylethylene and its halogen derivatives indicates *in vivo* hydroxylation. Presumably the halogen atom aids this, but in the absence of some information concerning the mechanism of hydroxylation *in vivo* it is not possible to decide whether an inductive or a mesomeric effect of the halogen could aid hydroxylation. In view of what has been said previously concerning the importance of the hydroxyl group to the estrogenic function, the idea of *in vivo* hydroxylation of these triphenylethylenes seems preferable. 2-Ethyl-1,1,2-triphenylethylene (CLI) is quite active (115), suggesting that a steric effect of the ethyl group results in a closer resemblance of this molecule to that of diethylstilbestrol and is responsible for the increased activity relative to triphenylethylene. A steric effect is probably a second function of the halogen atom of the triphenylhalogenoethylenes. Rinderknecht and Rowe (357) prepared a series of 1,1,2-triphenylethylenes and ethanes which were substituted in the aliphatic portion and found CLII to have about 66 per cent of the activity of estrone similarly tested. The piperidino ether (CLIII) was surprisingly active, having about 30 per cent of the activity of estrone.

(c) Variation of the aliphatic portion and of aromatic substitution

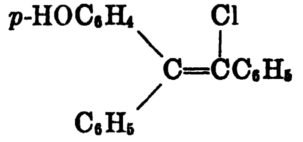
9,α-Chlorobenzylidenefluorene (CLIV) is much less active than the corresponding chlorotriphenylethylene (144); this result would appear to emphasize the importance of the halogen as a steric factor. 2-Bromo-1-(*p*-ethylphenyl)-1,2-diphenylethylene (CLV) is active at 0.1 mg. (251); in view of the previous discussion this suggests that the unsubstituted rings have a trans relation and will presumably be hydroxylated *in vivo*. As for triphenylethylene itself, the introduction of hydroxyl groups into triphenylhalogenoethylenes enhances the estrogenic potency of the latter (115). Both geometrical isomers of 2-chloro-1-(*p*-hydroxyphenyl)-1,2-diphenylethylene (CLVI) are quite active (115) and of the same order. However, this is not necessarily unexpected, since the 2-phenyl group in both isomers will probably need to be hydroxylated; in view of the suggested function of a halogen atom this ring is probably most difficult to hydroxylate biochemically. 1,1-Bis(*p*-hydroxyphenyl)-2-chloro-2-phenylethylene (CLVII) (115) gives 50 per cent response in mice subcutaneously at 0.2 microgram, an increase in potency over the corresponding monohydroxy compound. The dimethyl ether of CLVII in accordance with generality is two hundred times less active than the free phenol. 1,2-Tris(*p*-bromophenyl)-2-chloroethylene (CLVIII) is active, and its action is prolonged (480). This compound, however, is less prolonged in action than the corresponding 1,1,2-tris(*p*-bromophenyl)ethylene (480). This conclusion seems to apply to various similar halogen derivatives. Again it would seem that the para halogen atoms in CLVIII and related compounds are replaced biochemically by hydroxyl groups.



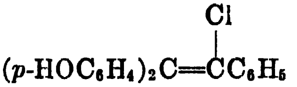
CLIV



CLV

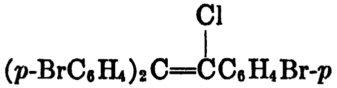


CLVI



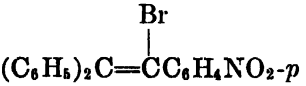
$(p\text{-}HOC_6H_4)_2C{=}\overset{\overset{Cl}{|}}{C}C_6H_5$

CLVII



$(p\text{-}BrC_6H_4)_2C{=}\overset{\overset{Cl}{|}}{C}C_6H_4Br\text{-}p$

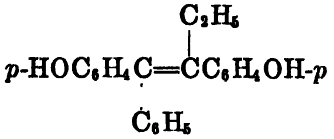
CLVIII



$(C_6H_5)_2C{=}\overset{\overset{Br}{|}}{C}C_6H_4NO_2\text{-}p$

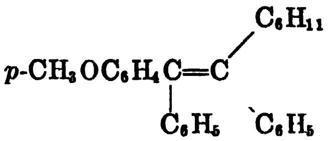
CLIX

2-Bromo-1-(*p*-methylthiophenyl)-1,2-diphenylethylene is active at 1 mg. (301), but 2-bromo-1,1-bis(*p*-methylthiophenyl)-2-phenylethylene is inactive at 5 mg. (558); apparently in this series methylthio groups are unsuitable. It is interesting that 2-bromo-2-(*p*-nitrophenyl)-1,1-diphenylethylene (CLIX) is active (52) at 1 mg.; it would be valuable to have a comparison with the corresponding amino acompound. 1,2-Bis(*p*-hydroxyphenyl)-2-ethyl-2-phenylethylene (CLX) (115) is very potent, giving 50 per cent response in mice subcutaneously at 0.9 microgram; it is apparently the most potent triphenylethylene derivative known. Its high activity is hardly surprising, since it must have a close structural resemblance to diethylstilbestrol. The highly substituted compound 2-cyclohexyl-1-(*p*-methoxyphenyl)-1,2-diphenylethylene (CLXI) and the corresponding ethoxy compound have slight activity (168). The reported triphenylethylenes of estrogenic interest are collected in tables 17 and 18. It may be pointed out that the estrogenic activities of many triphenylethylenes have been reported in terms of the duration of estrus produced by a given dosage of estrogen (359).



$p\text{-HOC}_6\text{H}_4\text{C}(\text{C}_6\text{H}_5){=}\text{C}(\text{C}_2\text{H}_5)\text{C}_6\text{H}_4\text{OH-}p$

CLX



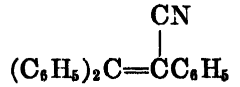
$p\text{-CH}_3\text{OC}_6\text{H}_4\text{C}(\text{C}_6\text{H}_5){=}\text{C}(\text{C}_6\text{H}_{11})\text{C}_6\text{H}_5$

CLXI

F. TRIPHENYLACRYLONITRILE AND ITS ANALOGS

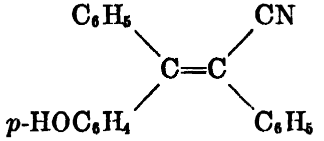
Although triphenylacrylonitrile and related compounds are closely related structurally to the triphenylethylenes, the extensive work in this field justifies their separate consideration. The study of the estrogenic triphenylacrylonitriles is of more recent origin and is almost wholly due to the efforts of Buu-Hoï, Lacassagne, and their collaborators.

Triphenylacrylonitrile (CLXII) itself has been reported, by the same group (251), as having the same activity as triphenylethylene when used subcutaneously in mice, 0.1 mg. of each giving full response. The reports of other workers appear to indicate that triphenylacrylonitrile is more active (209) than triphenylethylene. The linear cyano group can have no steric effect on the triphenylethylene system, and it seems that it can only have an effect on some physical property of the molecule.

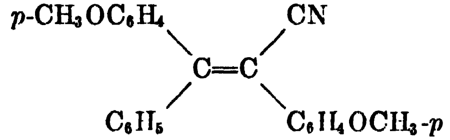


$(\text{C}_6\text{H}_5)_2\text{C}{=}\text{C}(\text{CN})\text{C}_6\text{H}_5$

CLXII



CLXIII



CLXIV

Replacement of the cyano group by the carboxyl group decreases estrogenic potency (251) and use of the amido group abolishes activity (78). In contrast to the effect in the triphenylethylene series the introduction of a hydroxyl or potential hydroxyl group into triphenylacrylonitrile has little effect on activity. β-(*p*-Hydroxyphenyl)-α,β-diphenylacrylonitrile (CLXIII) (45) and *trans*-α,β-bis(*p*-methoxyphenyl)-β-phenylacrylonitrile (CLXIV) (78) have the same activity in mice as the parent compound. Various modifications of triphenylacrylonitrile may be made without removing estrogenic activity.

TABLE 17

Triphenylethylene analogs with variation of aromatic substitution

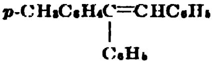
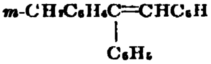
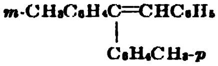
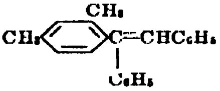
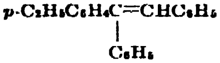
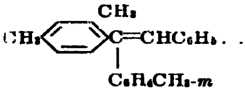
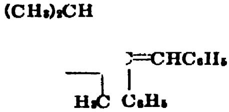
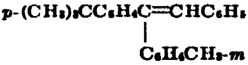
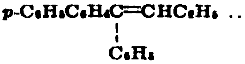
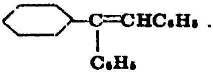
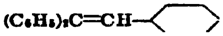
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise
	°C.	
$(C_6H_5)_2C=CHC_6H_5$		300* (50%) > 200*§ (50%) 0.1 mg.* 10 mg.‖
 $p\text{-}CH_3C_6H_4\underset{\underset{\displaystyle C_6H_5}{\vert}}{C}=CHC_6H_5$	238–240/20 mm. (b.p.)	
 $m\text{-}CH_3C_6H_4\underset{\underset{\displaystyle C_6H_5}{\vert}}{C}=CHC_6H$	240–242/20 mm. (b.p.)	
 $m\text{-}CH_3C_6H_4\underset{\underset{\displaystyle C_6H_4CH_3\text{-}p}{\vert}}{C}=CHC_6H_5$	248–250/22 mm. (b.p.)	
	198–200/1 8 mm. (b.p.)	1 mg.*
 $p\text{-}C_2H_5C_6H_4\underset{\underset{\displaystyle C_6H_5}{\vert}}{C}=CHC_6H_5$	200–202/2 mm. (b.p.)	1 mg.*
	245–248/15 mm. (b.p.)	> 1 mg.*
$p\text{-}(CH_3)_3CC_6H_4\underset{\underset{\displaystyle C_6H_5}{\vert}}{C}=CHC_6H_5$	260–262/22 mm. (b.p.)	
	245–248/1 mm. (b.p.)	
 $p\text{-}(CH_3)_3CC_6H_4\underset{\underset{\displaystyle C_6H_4CH_3\text{-}m}{\vert}}{C}=CHC_6H_5$	218–220/2.1 mm. (b.p.)	
 $p\text{-}C_6H_5C_6H_4\underset{\underset{\displaystyle C_6H_5}{\vert}}{C}=CHC_6H_5$ ..	177.5	
$(p\text{-}C_6H_5C_6H_4)_2C=CHC_6H_5$		10 mg.* (inactive)
.	141/0.14 mm. (b.p.) 137–138/0.3 mm. (b.p.)	Inactive
........		Active*

TABLE 17—*Continued*

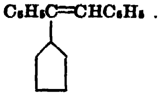
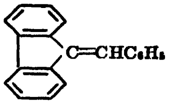
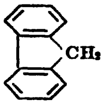
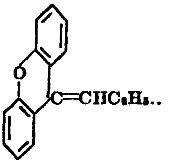
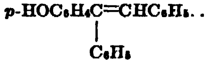
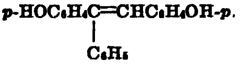
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
$(C_6H_{11})_2C{=}CHC_6H_5$	39		(372)
 $C_6H_5C{=}CHC_6H_5$	118–120/9 × 10⁻³ mm. (b.p.)	Inactive	(168)
	75–76	100 mg. (inactive) 50 mg. (weakly active)	(209) (144)
		100 mg. (inactive)	(144)
	114–114.5	100 mg. (inactive)	(209)
 $p\text{-}HOC_6H_4\underset{\underset{C_6H_5}{\vert}}{C}{=}CHC_6H_5$		20* (50%) 44*§ (50%)	(115) (115)
$(p\text{-}HOC_6H_4)_2C{=}CHC_6H_5$	178	50* (slight effect)	(483)
		75* (2 days)¶	(483)
		100* (2 days)¶	(483)
		200* (3 days)¶	(483)
		375* (3 days)¶	(483)
		750* (4 days)¶	(483)
		1000*† (nil)¶	(483)
		8* (50%)	(115)
		20*§ (50%)	(115)
	178		(477)
	179–181	(266)	(266)
Methyl ethyl ether	240–250/15 mm. (b.p.)		(15)
Diethyl ether	74–75		(16)
Di-*n*-propyl ether	76–77		(477)
Diisopropyl ether	83–84		(477, 478)
Diallyl ether	71–73		(477, 478)
Dibenzyl ether	94		(477, 478)
Diacetate	84	1000* (9 days)¶	(483)
Dipropionate	65–66	100* (6 days)¶	(483)
$(p\text{-}CH_3OC_6H_4)_2CHCH_2C_6H_5$	98	2 mg.*	(45)
 $p\text{-}HOC_6H_4\underset{\underset{C_6H_5}{\vert}}{C}{=}CHC_6H_4OH\text{-}p$		15* (50%) 10*§ (50%)	(115) (115)
$(p\text{-}HOC_6H_4)_2C{=}CHC_6H_4OH\text{-}p$	189–191		(396)
Triacetate	135–137		(396)
Trimethyl ether	100–101		(396, 397)
Triethyl ether	88		(480)

TABLE 17—*Continued*

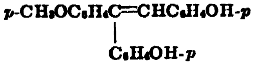
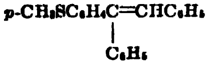
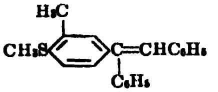
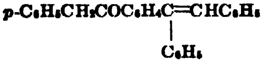
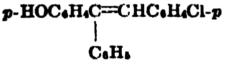
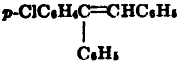
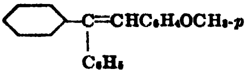
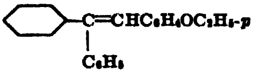
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
$(p\text{-}HOC_6H_4)_2C{=}CHC_6H_4OCH_3\text{-}p$	184–185		(396)
$(p\text{-}CH_3OC_6H_4)_2C{=}CHC_6H_4OH\text{-}p$			(396)
 $p\text{-}CH_3OC_6H_4\underset{\displaystyle C_6H_4OH\text{-}p}{\underset{\mid}{C}}{=}CHC_6H_4OH\text{-}p$			(396)
$(p\text{-}C_6H_5CH_2OC_6H_4)_2C{=}CHC_6H_4OCH_3\text{-}p$	80–82		(396)
$(p\text{-}CH_3OC_6H_4)_2C{=}CHC_6H_4OCH_2C_6H_5\text{-}p$	139–141		(396)
$(p\text{-}C_3H_7OC_6H_4)_2C{=}CHC_6H_4OC_2H_5\text{-}h$	76		(59)
 $p\text{-}CH_3SC_6H_4\underset{\displaystyle C_6H_5}{\underset{\mid}{C}}{=}CHC_6H_5$	100		(49)
$(p\text{-}CH_3SC_6H_4)_2C{=}CHC_6H_5$	106	1 mg.* (inactive)	(301)
		1 mg.*† (inactive)	(301)
	112		(558)
	280/17 mm. (b.p.)		(49)
$[p\text{-}(CH_3)_2NC_6H_4]_2C{=}CHC_6H_5$		5 mg.* (inactive)	(78)
$[p\text{-}(CH_3)_2NC_6H_4]_2C{=}CHC_6H_4OCH_3\text{-}p$	125–126		(397)
$(p\text{-}CH_3OC_6H_4)_2C{=}CHC_6H_4COOH\text{-}p$	204.5–205.5	1 mg. (inactive)	(303)
$(C_6H_5)_2C{=}CHC_6H_4CN\text{-}p$	107–109	1 mg.* (weakly active)	(480)
$(p\text{-}CNC_6H_4)_2C{=}CHC_6H_5$	151	5 mg.* (∞) ¶	(480)
 $p\text{-}C_6H_5CH_2COC_6H_4\underset{\displaystyle C_6H_5}{\underset{\mid}{C}}{=}CHC_6H_5$	110–111	5 mg.* (∞) ¶	(480)
$(C_6H_5)_2C{=}CHC_6H_4COCH_3\text{-}p$	125	0.1 mg.	(52)
$(C_6H_5)_2C{=}CHC_6H_4COC_2H_5\text{-}p$	85	1 mg.	(52)
 $p\text{-}HOC_6H_4\underset{\displaystyle C_6H_5}{\underset{\mid}{C}}{=}CHC_6H_4Cl\text{-}p$	139–140		(266)
$(p\text{-}CH_3OC_6H_4)_2C{=}CHC_6H_4Cl\text{-}p$	91	1000* (3 days) ¶	(482)
$(p\text{-}C_2H_5OC_6H_4)_2C{=}CHC_6H_4Cl\text{-}p$	76	1000* (weakly active)	(482)
$(p\text{-}CH_3OC_6H_4)_2C{=}CHC_6H_4Br\text{-}p$	107		(480)
$(p\text{-}C_2H_5OC_6H_4)_2C{=}CHC_6H_4Br\text{-}p$	110	1 mg.* (<125 days) ¶	(480)
$(C_6H_5)_2C{=}CHC_6H_4Cl\text{-}p$	76–77		(482)
 $p\text{-}ClC_6H_4\underset{\displaystyle C_6H_5}{\underset{\mid}{C}}{=}CHC_6H_5$	89		(52)
$(C_6H_5)_2C{=}CHC_6H_4Br\text{-}p$	77	1000* (2 days) ¶	(482)
$(p\text{-}ClC_6H_4)_2C{=}CHC_6H_4Cl\text{-}p$	90–91		(482)
$(p\text{-}ClC_6H_4)_2C{=}CHC_6H_4Br\text{-}p$	118	5 mg.* (∞) ¶	(480)
$(p\text{-}ClC_6H_4)_2C{=}CHC_6H_4CH_3\text{-}p$	94	5 mg.* (∞) ¶	(480)
$(p\text{-}BrC_6H_4)_2C{=}CHC_6H_4Cl\text{-}p$	84		(482)
$(p\text{-}BrC_6H_4)_2C{=}CHC_6H_4Br\text{-}p$	101	5 mg.* (∞) ¶	(480)
$(p\text{-}IC_6H_4)_2C{=}CHC_6H_4Cl\text{-}p$	102–103		(482)
	79	Inactive	(168)
	57–58	Inactive	(168)

TABLE 17—*Continued*

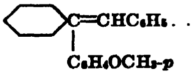
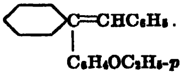
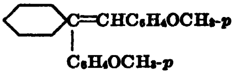
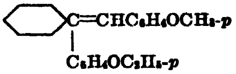
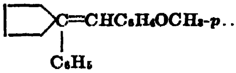
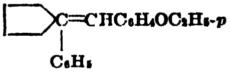
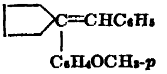
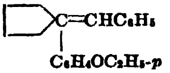
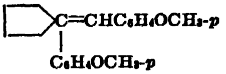
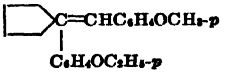
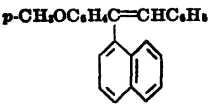
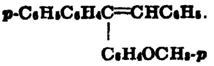
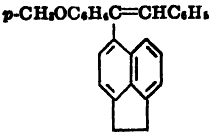
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°*C.*		
 $\mathrm{C{=}CHC_6H_5}$ $\mathrm{C_6H_4OCH_3}$-*p*	108/4.7 × 10^{-5} mm. (b.p.)	Inactive	(168)
 $\mathrm{C{=}CHC_6H_5}$ $\mathrm{C_6H_4OC_2H_5}$-*p*	118/1.3 × 10^{-4} mm. (b.p.)	Inactive	(168)
 $\mathrm{C{=}CHC_6H_4OCH_3}$-*p* $\mathrm{C_6H_4OCH_3}$-*p*	168–174/5 × 10^{-2} mm. (b.p.)		(168)
 $\mathrm{C{=}CHC_6H_4OCH_3}$-*p* $\mathrm{C_6H_4OC_2H_5}$-*p*	168/3 × 10^{-3} mm (b.p.)		(168)
 $\mathrm{C{=}CHC_6H_4OCH_3}$-*p* $\mathrm{C_6H_5}$	78–79	Inactive	(168)
 $\mathrm{C{=}CHC_6H_4OC_2H_5}$-*p* $\mathrm{C_6H_5}$	100–102/2 × 10^{-3} mm. (b.p.)	Inactive	(168)
 $\mathrm{C{=}CHC_6H_5}$ $\mathrm{C_6H_4OCH_3}$-*p*	104/1.3 × 10^{-4} mm. (b.p.)	Inactive	(168)
 $\mathrm{C{=}CHC_6H_5}$ $\mathrm{C_6H_4OC_2H_5}$-*p*	114/7 × 10^{-4} mm. (b.p.)	Inactive	(168)
 $\mathrm{C{=}CHC_6H_4OCH_3}$-*p* $\mathrm{C_6H_4OCH_3}$-*p*	165/1.5 × 10^{-3} mm. (b.p.)		(168)
 $\mathrm{C{=}CHC_6H_4OCH_3}$-*p* $\mathrm{C_6H_4OC_2H_5}$-*p*	164/4.7 × 10^{-3} mm. (b.p.)		(168)
 *p*-$\mathrm{CH_3OC_6H_4C{=}CHC_6H_5}$	102	1 mg.*	(47) (79)
 *p*-$\mathrm{C_6H_5C_6H_4C{=}CHC_6H_5}$ $\mathrm{C_6H_4OCH_3}$-*p*	102	10 mg.* 2 mg.* (incompletely active)	(47) (79) (79)
 *p*-$\mathrm{CH_3OC_6H_4C{=}CHC_6H_5}$		2 mg.*	(79)

TABLE 17—*Continued*

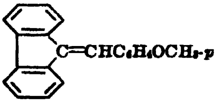
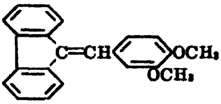
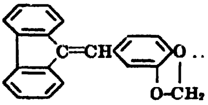
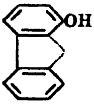
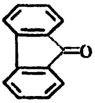
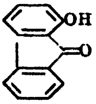
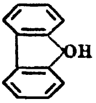
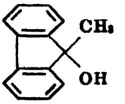
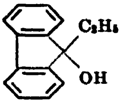
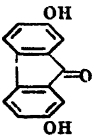
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°*C.*		
	128–128.5	100 mg. (inactive) 50 mg. (weakly active)	(209) (144)
		50 mg. (weakly active)	(144)
		50 mg. (weakly active)	(144)
		100 mg. (inactive)	(144)
		100 mg. (inactive)	(144)
		100 mg. (inactive)	(144)
Benzoate		100 mg. (inactive)	(144)
		100 mg. (inactive)	(144)
		100 mg. (inactive)	(144)
		100 mg. (inactive)	(144)
		100 mg. (weakly active)	(144)

TABLE 17—*Concluded*

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°*C.*		
Dibenzoate		100 mg. (weakly active)	(144)
Dimethyl ether		100 mg. (inactive)	(144)
$(p\text{-}CH_3OC_6H_4)_2C{=}CH_2$	142–143		(341)
		5 mg * (inactive)	(481)
$(p\text{-}C_2H_5OC_6H_4)_2C{=}CH_2$	142		(481)
$(p\text{-}C_3H_7OC_6H_4)_2C{=}CH_2$	54		(481)
$(p\text{-}C_6H_5CH_2OC_6H_4)_2C{=}CH_2$	186		(481)
$(p\text{-}C_2H_5OC_6H_4)_2C{=}CHCOOH$	134		(480)
$(p\text{-}C_3H_7OC_6H_4)_2C{=}CHCOOH$	128-129		(480)

* In mice.

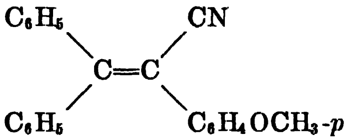
† Orally.

§ Administered intravaginally.

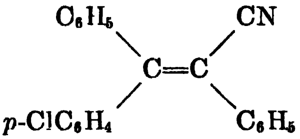
‖ Administered in divided dosage over a period of 2.5 days.

¶ The period of median duration of estrus.

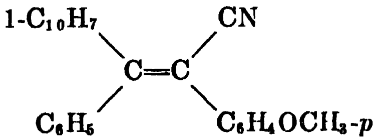
β,β-Diphenyl-α-(*p*-tolyl)acrylonitrile (CLXV) (251) is active at 1 mg. in mice subcutaneously; *trans*-β-(*p*-chlorophenyl)-α,β-diphenylacrylonitrile (CLXVI) is active at the same level (251). Replacement of a β-phenyl group by various polycyclic groups is possible without destroying activity, and *cis*-α-(*p*-methoxyphenyl)-β-(1-naphthyl)-β-phenylacrylonitrile (CLXVII) is one of the most active acrylonitriles, being active in the rat subcutaneously at 0.01 mg. (46).



CLXV



CLXVI



CLXVII

The data relating to the estrogenic activities of the various acrylonitriles are collected in table 19.

VII. RING-CLOSED ANALOGS OF DIETHYLSTILBESTROL, HEXESTROL, AND DIENESTROL

Various chrysene, phenylnaphthalene, and phenylindene derivatives (462) were synthesized earlier as ring-closed analogs of the stilbene estrogens. It was thought that these ring-closed structures would more closely simulate the general

TABLE 18

Triphenylethylene analogs with variation of the aliphatic portion and aromatic substitution

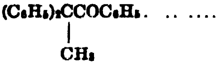
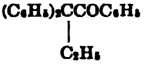
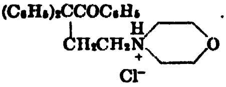
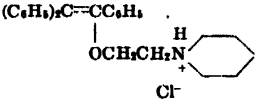
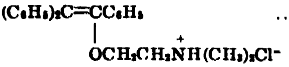
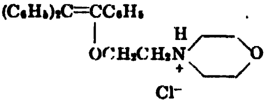
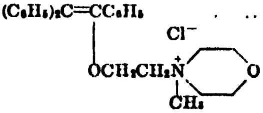
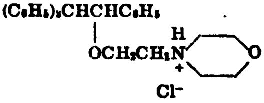
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
A. Variation of the aliphatic portion			
	°C.		
$(C_6H_5)_2C{=}C(C_6H_5)Cl$		77* (50%)	(115)
		0.89*§ (50%)	(115)
		29	(14)
$(C_6H_5)_2C{=}C(C_6H_5)Br$		<0.01 mg.*	(251)
		33.5 (incomplete)	(14)
$(C_6H_5)_2C{=}C(C_6H_5)I$	125	38.2 (incomplete)	(14)
$(C_6H_5)_2C{=}C(C_6H_5)C_2H_5$		12* (50%)	(115)
		4.4*§ (50%)	(115)
$(C_6H_5)_2CHCOC_6H_5$		10‖ (I.U./mg.)	(357)
		40** (I.U./mg.)	(357)
 $(C_6H_5)_2C(CH_3)COC_6H_5$		6000 (I.U./mg.)	(357)
 $(C_6H_5)_2C(C_2H_5)COC_6H_5$		1000 (I.U./mg.)	(357)
		<100 (I.U./mg.)	(357)
$(C_6H_5)_2C{=}C(C_6H_4)OCOCH_3$		400‖ (I.U./mg.)	(357)
		400** (I.U./mg.)	(357)
$(C_6H_5)_2C{=}C(C_6H_4)OC_2H_5$		5000 (I.U./mg.)	(357)
$(C_6H_5)_2C{=}C(C_6H_4)OC_3H_7$		500 (I.U./mg.)	(357)
		3000 (I.U./mg.)	(357)
 $(C_6H_5)_2C{=}CC_6H_4OCH_2CH_2\overset{+}{N}H(CH_3)_2Cl^-$		200 (I.U./mg.)	(357)
		100 (I.U./mg.)	(357)
		<400‖ (I.U./mg.) <100** (I.U./mg.)	
		<400 (I.U./mg.)	(357)

TABLE 18—*Continued*

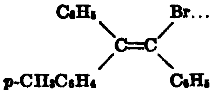
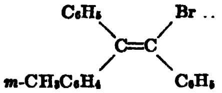
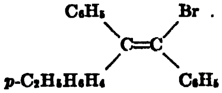
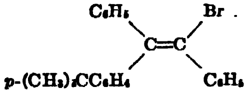
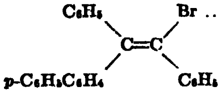
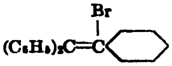
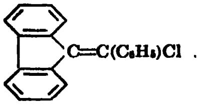
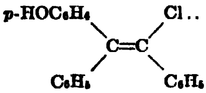
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Variation of the aliphatic portion and aromatic substitution			
	°C.		
	113.5–114		(44)
		0.01 mg.*	(251)
	Cis-trans mixture		(44)
	112.5–113		(44)
		0.1 mg.*	(251)
		1 mg.*	(251)
	181–182 (d.)		(44)
		0.1 mg.*	(251)
	112	1 mg.*	(362)
		20 mg.* (15 days)¶	(362)
		50 mg. (strongly active)	(144)
	101–103		
	136–138 (β-form)		
			(266)
			(266)
		2.3* (50%)	(115)
		0.0014*§ (50%)	(115)
		1.6* (50%) (isomeric form)	(115)
		0.0013§ (50%) (isomeric form)	(115)
$(p\text{-}HOC_6H_4)_2C{=}C(C_6H_5)Cl$		0.2* (50%)	(115)
		0.0010*§ (50%)	(115)
Dimethyl ether		40* (50%)	(115)
		1.2*§ (50%)	(115)
Ethyl methyl ether	210–220/1 mm. (b.p.)		(15)
Diethyl ether	86–88		(477)
Dipropyl ether	102		(477)
Diisopropyl ether	106		(477)

TABLE 18—*Continued*

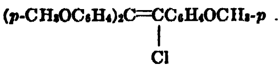
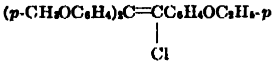
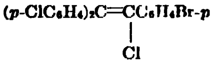
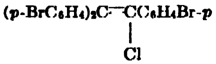
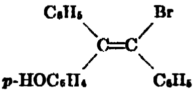
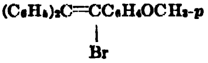
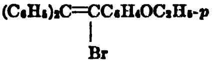
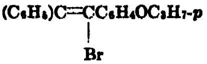
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Variation of the aliphatic portion and aromatic substitution—*Continued*			
	°C.		
 $(p\text{-CH}_3\text{OC}_6\text{H}_4)_2\text{C}{=}\underset{\text{Cl}}{\underset{\vert}{\text{C}}}\text{C}_6\text{H}_4\text{OCH}_3\text{-}p$	113–114		(397)
		1 mg.† (2 days) ¶	(504)
		5 mg.† (17 days) ¶	(504)
		1 mg. (53 days) ¶	(504)
		6 mg.††	(367)
 $(p\text{-CH}_3\text{OC}_6\text{H}_4)_2\text{C}{=}\underset{\text{Cl}}{\underset{\vert}{\text{C}}}\text{C}_6\text{H}_4\text{OC}_2\text{H}_5\text{-}p$	82		(166)
 $(p\text{-ClC}_6\text{H}_4)_2\text{C}{=}\underset{\text{Cl}}{\underset{\vert}{\text{C}}}\text{C}_6\text{H}_4\text{Br-}p$	170–171	5 mg.* (12 days) ¶	(480)
 $(p\text{-BrC}_6\text{H}_4)_2\text{C}{=}\underset{\text{Cl}}{\underset{\vert}{\text{C}}}\text{C}_6\text{H}_4\text{Br-}p$	189	1 mg.* (11 days) ¶	(480)
		5 mg.* (15 days) ¶	(480)
$(p\text{-C}_2\text{H}_5\text{OC}_6\text{H}_4)_2\text{C}{=}\text{CHCl}$	76		(481)
$(p\text{-C}_3\text{H}_7\text{OC}_6\text{H}_4)_2\text{C}{=}\text{CHCl}$	Oil		(481)
$(p\text{-C}_6\text{H}_5\text{CH}_2\text{OC}_6\text{H}_4)_2\text{C}{=}\text{CHCl}$	98–99		(481)
	158–160		(266)
		2.7* (50%)	(115)
		0.011*§ (50%)	(115)
		3.0* (50%) (isomeric form)	(115)
		0.01*§ (50%) (isomeric form)	(115)
Methyl ether		105* (50%)	(115)
		0.70*§ (50%)	(115)
		100* (50%) (isomeric form)	(115)
		0.49*§ (50%) (isomeric form)	(115)
Ethyl ether	91–92		(59)
	83–84 (polymorphic form)		(59)
	111 (isomeric form)		(59)
Propyl ether	118		(59)
 $(\text{C}_6\text{H}_5)_2\text{C}{=}\underset{\text{Br}}{\underset{\vert}{\text{C}}}\text{C}_6\text{H}_4\text{OCH}_3\text{-}p$	130		(59)
 $(\text{C}_6\text{H}_5)_2\text{C}{=}\underset{\text{Br}}{\underset{\vert}{\text{C}}}\text{C}_6\text{H}_4\text{OC}_2\text{H}_5\text{-}p$	95		(59, 166)
 $(\text{C}_6\text{H}_5)\text{C}{=}\underset{\text{Br}}{\underset{\vert}{\text{C}}}\text{C}_6\text{H}_4\text{OC}_3\text{H}_7\text{-}p$	92		(59, 166)

TABLE 18—*Continued*

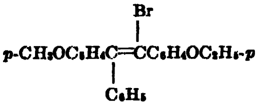
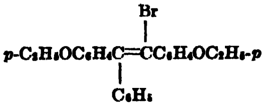
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Variation of the aliphatic portion and aromatic substitution—*Continued*			
	°*C.*		
$(p\text{-HOC}_6\text{H}_4)_2\text{C}{=}\text{C}(\text{C}_6\text{H}_5)\text{Br}$	205–207	1* (nil)	(483)
		2* (weakly active)	(483)
		10* (4 days)¶	(483)
		15* (5 days)¶	(483)
		100* (8 days)¶	(483)
		10*† (weakly active)	(483)
		20*† (3 days)¶	(483)
		25*† (3 days)¶	(483)
		50*† (3 days)¶	(483)
		100*† (3 days)¶	(483)
		0.54* (50%)	(115)
		0.0014*§ (50%)	(115)
	209–210 (d.)		(266)
	205–207		(477)
Diacetate	157–159	0.2* (weakly active)¶	(483)
		0.5* (5 days)¶	(483)
		1* (5 days)¶	(483)
		2* (5 days)¶	(483)
		10* (9 days)¶	(483)
		1000* (24 days)¶	(483)
		10*† (3 days)¶	(483)
		50*† (6 days)¶	(483)
Dimethyl ether		51* (50%)	(115)
		1.0*§ (50%)	(115)
			(387)
Ethyl methyl ether	78		(15)
Diethyl ether	96–97		(16)
	97		(59)
	87 (polymorphic form)		(59)
		10*† (7 days)¶	(482, 483)
		50*† (21 days)¶	(482, 483)
		500*† (38 days)¶	(482, 483)
		42.3 (incomplete)	(14)
Ethyl propyl ether	ca. 70 (isomer mixture)		(59, 167)
Dipropyl ether	101		(477)
Diisopropyl ether	119–120		(477)
		100* (6 days)	(483)
		1000* (128 days)	(483)
	100.5		(167)
Di-*sec*-butyl ether	88		(167)
 $p\text{-CH}_3\text{OC}_6\text{H}_4\underset{\text{C}_6\text{H}_5}{\text{C}}{=}\overset{\text{Br}}{\text{C}}\text{C}_6\text{H}_4\text{OC}_2\text{H}_5\text{-}p$	106		(59, 166)
	153 (isomeric form)		(59, 166)
 $p\text{-C}_2\text{H}_5\text{OC}_6\text{H}_4\underset{\text{C}_6\text{H}_5}{\text{C}}{=}\overset{\text{Br}}{\text{C}}\text{C}_6\text{H}_4\text{OC}_2\text{H}_5\text{-}p$	133–134		(16)

TABLE 18—*Continued*

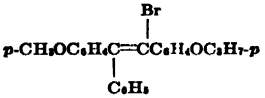
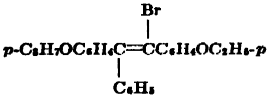
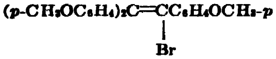
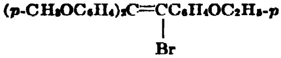
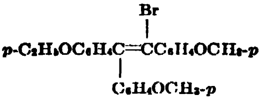
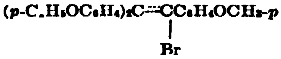
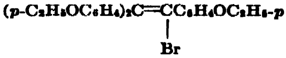
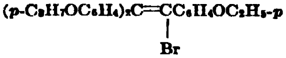
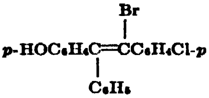
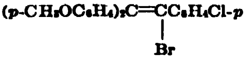
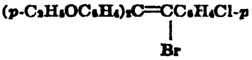
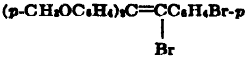
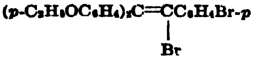
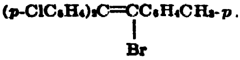
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Variation of the aliphatic portion and aromatic substitution—*Continued*			
	°*C.*		
 $p\text{-}CH_3OC_6H_4\underset{C_6H_5}{C}{=}\overset{Br}{C}C_6H_4OC_3H_7\text{-}p$	85		(59, 166)
 $p\text{-}C_3H_7OC_6H_4\underset{C_6H_5}{C}{=}\overset{Br}{C}C_6H_4OC_2H_5\text{-}p$	71		(59)
 $(p\text{-}CH_3OC_6H_4)_2C{=}\underset{Br}{C}C_6H_4OCH_3\text{-}p$	119–120.5		(397)
 $(p\text{-}CH_3OC_6H_4)_2C{=}\underset{Br}{C}C_6H_4OC_2H_5\text{-}p$	76		(59, 166)
 $p\text{-}C_2H_5OC_6H_4\underset{C_6H_4OCH_3\text{-}p}{C}{=}\overset{Br}{C}C_6H_4OCH_3\text{-}p$	136–138		(15)
 $(p\text{-}C_2H_5OC_6H_4)_2C{=}\underset{Br}{C}C_6H_4OCH_3\text{-}p$	81		(59)
 $(p\text{-}C_2H_5OC_6H_4)_2C{=}\underset{Br}{C}C_6H_4OC_2H_5\text{-}p$	81–82		(59, 166)
 $(p\text{-}C_3H_7OC_6H_4)_2C{=}\underset{Br}{C}C_6H_4OC_2H_5\text{-}p$	86		(59, 166)
 $p\text{-}HOC_6H_4\underset{C_6H_5}{C}{=}\overset{Br}{C}C_6H_4Cl\text{-}p$	141–143		(266)
 $(p\text{-}CH_3OC_6H_4)_2C{=}\underset{Br}{C}C_6H_4Cl\text{-}p$	112	100* (5 days) ¶ 10*† (weakly active) 100*† (16 days) ¶	(482) (482) (482)
 $(p\text{-}C_2H_5OC_6H_4)_2C{=}\underset{Br}{C}C_6H_4Cl\text{-}p$	98	100* (3 days) ¶ 10*† (3 days) ¶ 100*† (16 days) ¶	(482) (482) (482)
 $(p\text{-}CH_3OC_6H_4)_2C{=}\underset{Br}{C}C_6H_4Br\text{-}p$	114		(480)
 $(p\text{-}C_2H_5OC_6H_4)_2C{=}\underset{Br}{C}C_6H_4Br\text{-}p$	99	0.1 mg.* (8 days) ¶ 0.5 mg.* (>130 days) ¶	(480) (480)
 $(p\text{-}ClC_6H_4)_2C{=}\underset{Br}{C}C_6H_4CH_3\text{-}p$	158	5 mg.* (>90 days) ¶	(480)
$(C_6H_5)_2C{=}CC_6H_4Cl\text{-}p$	114–115	100* (11 days) ¶	(482)

TABLE 18—*Continued*

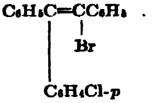
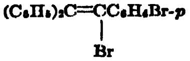
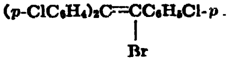
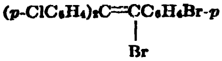
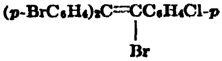
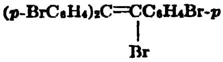
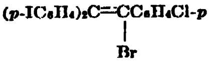
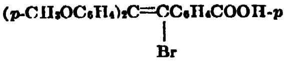
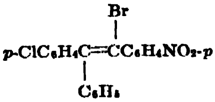
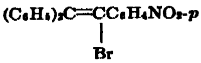
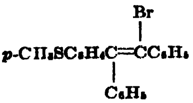
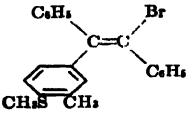
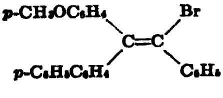
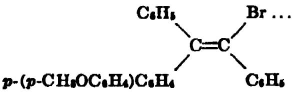
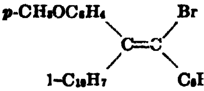
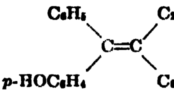
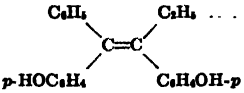
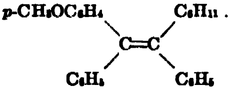
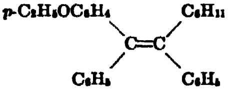
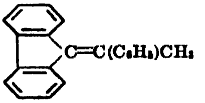
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Variation of the aliphatic portion and aromatic substitution—*Continued*			
	°C.		
 $\underset{C_6H_4Cl\text{-}p}{C_6H_5C}=\underset{Br}{C}C_6H_5$	157	5 mg.	(52)
 $(C_6H_5)_2C=\underset{Br}{C}C_6H_4Br\text{-}p$	114–115	1000* (56 days) ¶	(482)
 $(p\text{-}ClC_6H_4)_2C=\underset{Br}{C}C_6H_4Cl\text{-}p$	106	5000* (5 days) ¶	(443)
 $(p\text{-}ClC_6H_4)_2C=\underset{Br}{C}C_6H_4Br\text{-}p$	174		(480)
 $(p\text{-}BrC_6H_4)_2C=\underset{Br}{C}C_6H_4Cl\text{-}p$	168	5000* (10 days) ¶	(482)
 $(p\text{-}BrC_6H_4)_2C=\underset{Br}{C}C_6H_4Br\text{-}p$	183	1 mg.* (7 days) ¶	(480)
 $(p\text{-}IC_6H_4)_2C=\underset{Br}{C}C_6H_4Cl\text{-}p$	158–160	5000* (10 days) ¶	(482)
 $(p\text{-}CH_3OC_6H_4)_2C=\underset{Br}{C}C_6H_4COOH\text{-}p$	197–198	1 mg. (inactive)	(303)
 $p\text{-}ClC_6H_4\underset{C_6H_5}{C}=\overset{Br}{C}C_6H_4NO_2\text{-}p$	163		(52)
 $(C_6H_5)_2C=\underset{Br}{C}C_6H_4NO_2\text{-}p$	180	0.1 mg.	(52)
 $p\text{-}CH_3SC_6H_4\underset{C_6H_5}{C}=\overset{Br}{C}C_6H_5$	131		(49)
	105	1 mg.*	(301)
$(p\text{-}CH_3SC_6H_4)_2C=C(C_6H_5)Br$	133	5 mg. (inactive)	(558)
$(p\text{-}C_2H_5SC_6H_4)_2C=C(C_6H_5)Br$	74		(362)
	124		(49)
	138–140	0.1 mg.*	(47) (79)

TABLE 18—*Concluded*

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Variation of the aliphatic portion and aromatic substitution—*Concluded*			
	°C.		
 C_6H_5 Br C=C p-(p-$CH_3OC_6H_4$)C_6H_4 C_6H_5		1 mg.*	(79)
			(47)
		7.7* (50%) 0.015*§ (50%)	(115) (115)
 C_6H_5 C_2H_5 C=C p-HOC_6H_4 C_6H_4OH-p		0.9* (50%) 0.00065*§ (50%)	(115) (115)
 p-$CH_3OC_6H_4$ C_6H_{11} C=C C_6H_5 C_6H_5	127–127.5	Weakly active	(168)
 p-$C_2H_5OC_6H_4$ C_6H_{11} C=C C_6H_5 C_6H_5	127.5–129.5	Weakly active	(168)
		50 mg. (weakly active)	(144)
(p-$CH_3OC_6H_4$)$_2$C=CHBr	84	5 mg.* (inactive)	(481)
(p-$C_2H_5OC_6H_4$)$_2$C=CHBr	64		(481)
(p-$C_3H_7OC_6H_4$)$_2$C=CHBr	42		(481)
(p-$C_6H_5CH_2OC_6H_4$)$_2$C=CHBr	119–120		(481)

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* In mice.

† Orally.

§ Administered intravaginally.

‖ Administered in aqueous ethanol.

** Administered in peanut oil.

¶ The period of median duration of estrus.

†† Administered in four daily doses; produced cornification of the human female vagina.

TABLE 19

Estrogenic activities of triphenylacrylonitrile and its analogs

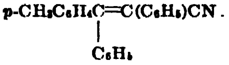
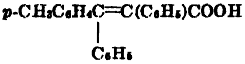
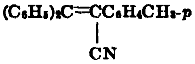
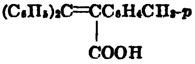
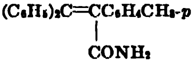
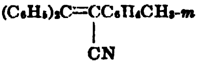
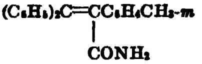
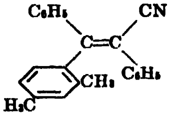
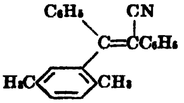
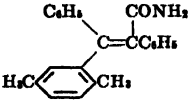
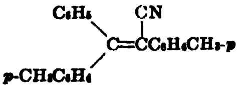
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose	References
	°C.		
$(C_6H_5)_2C{=}C(C_6H_5)CN$		0.1 mg.*	(251)
$(C_6H_5)_2C{=}C(C_6H_5)COOH$	213	5 mg.*	(50) (251)
$(C_6H_5)_2C{=}C(C_6H_5)CONH_2$		10 mg.* (inactive)	(78)
 $p\text{-}CH_3C_6H_4\underset{\underset{C_6H_5}{\vert}}{C}{=}C(C_6H_5)CN$	123		(50)
 $p\text{-}CH_3C_6H_4\underset{\underset{C_6H_5}{\vert}}{C}{=}C(C_6H_5)COOH$	208–210		(50)
 $(C_6H_5)_2C{=}\underset{\underset{CN}{\vert}}{C}C_6H_4CH_3\text{-}p$	153	1 mg.*	(50) (251)
 $(C_6H_5)_2C{=}\underset{\underset{COOH}{\vert}}{C}C_6H_4CH_3\text{-}p$	237–238	1 mg.*	(50) (78)
 $(C_6H_5)_2C{=}\underset{\underset{CONH_2}{\vert}}{C}C_6H_4CH_3\text{-}p$	216		(50)
 $(C_6H_5)_2C{=}\underset{\underset{CN}{\vert}}{C}C_6H_4CH_3\text{-}m$	122	1 mg.*	(50) (251)
 $(C_6H_5)_2C{=}\underset{\underset{CONH_2}{\vert}}{C}C_6H_4CH_3\text{-}m$	177		(50)
	134		(47)
	133		(47)
	ca. 203–204		(47)
	114–115	1 mg.*	(50) (78)

TABLE 19—*Continued*

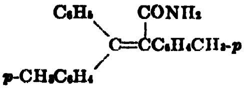
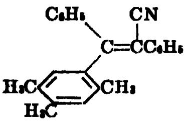
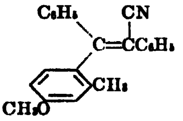
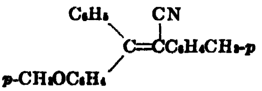
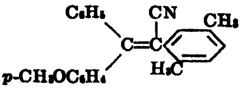
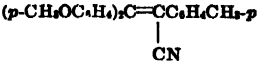
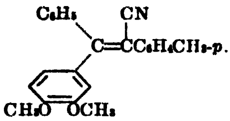
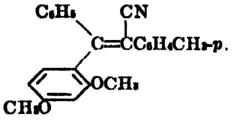
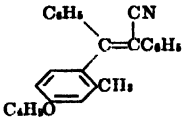
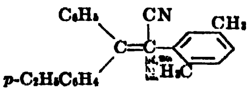
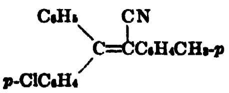
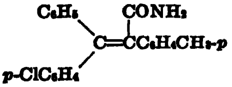
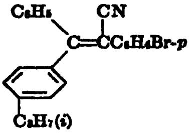
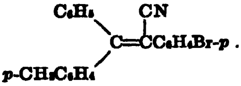
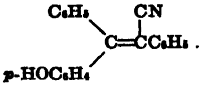
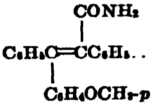
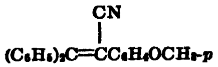
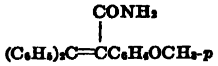
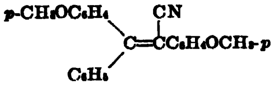
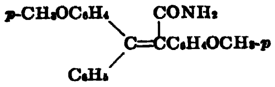
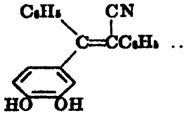
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose	References
	°C.		
	237		(50)
	>230/10 mm. (b.p.)		(47)
	134–135		(47)
	113–115		(51)
		1 mg.* (inactive)	(45)
 $(p\text{-}CH_3OC_6H_4)_2C{=}C(CN)C_6H_4CH_3\text{-}p$	110–111	0.1 mg.*	(50) (78)
	165–166		(51)
	200–202 (cis form)		(51)
		1 mg.*	(45)
		2 mg.* (inactive)	(45)
	147–148		(50)

TABLE 19—*Continued*

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose	References
	°C.		
 $(C_6H_5)(p\text{-}ClC_6H_4)C{=}C(CONH_2)C_6H_4CH_3\text{-}p$	197		(50)
		1 mg.* (inactive)	(45)
 $(C_6H_5)(p\text{-}CH_3C_6H_4)C{=}C(CN)C_6H_4Br\text{-}p$		2 mg.*	(45)
 $(C_6H_5)(p\text{-}HOC_6H_4)C{=}C(CN)C_6H_5$		0.1 mg.*	(45)
Methyl ether	166 (cis form)		(50)
	124–125 (trans form)		(50)
n-Propyl ether	129–130		(47)
		0.1 mg.*	(79)
		1 mg.* (1 month)¶	(79)
	105 (isomeric form)		
n-Butyl ether	114		(47)
		0.1 mg.*	(79)
 $C_6H_5C(C_6H_4OCH_3\text{-}p){=}C(CONH_2)C_6H_5$	196–198 (cis form) 176–180 (trans form)		(50)
 $(C_6H_5)_2C{=}C(CN)C_6H_4OCH_3\text{-}p$	149		(50)
		0.1 mg.*	(251)
 $(C_6H_5)_2C{=}C(CONH_2)C_6H_4OCH_3\text{-}p$	198		(50)
 $(p\text{-}CH_3OC_6H_4)(C_6H_5)C{=}C(CN)C_6H_4OCH_3\text{-}p$	122–125 (trans form)		(50)
		0.1 mg.*	(78)
 $(p\text{-}CH_3OC_6H_4)(C_6H_5)C{=}C(CONH_2)C_6H_4OCH_3\text{-}p$	243 (trans form)		(50)
		2 mg.* (incomplete)	(45)
Dimethyl ether	181 (cis form)		(50)

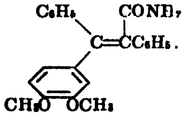
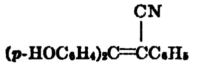
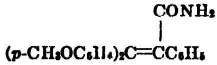
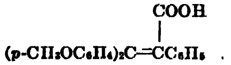
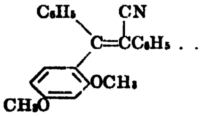
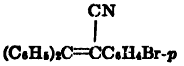
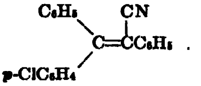
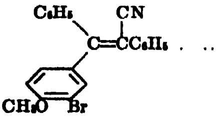
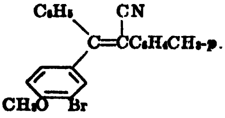
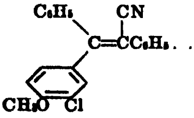
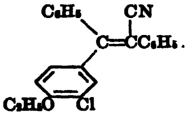
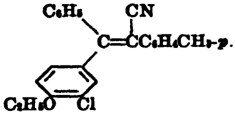
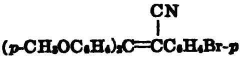
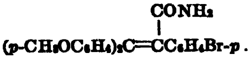
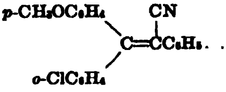
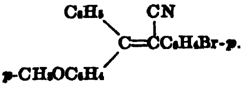
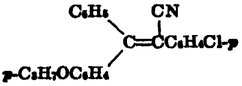
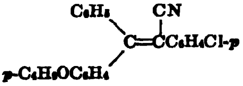
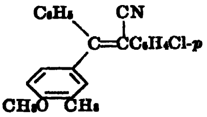
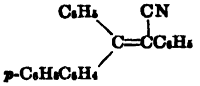
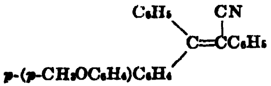
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose	References
	°C.		
		1 mg.*	(78)
	143–145 (trans form)		(50)
	198 (trans form)		(50)
 $(p\text{-}HOC_6H_4)_2C=\overset{CN}{C}C_6H_5$		<0.75 mg.*	(45)
Dimethyl ether	159		(50)
		0.01 mg.*	(251)
Diethyl ether	130–131		(51)
 $(p\text{-}CH_3OC_6H_4)_2C=\overset{CONH_2}{C}C_6H_5$	209		(50)
		3 mg.* (inactive)	(78)
 $(p\text{-}CH_3OC_6H_4)_2C=\overset{COOH}{C}C_6H_5$	169		(51)
		1 mg.*	(251)
	146–148		(50)
		1 mg.*	(78)
 $(C_6H_5)_2C=\overset{CN}{C}C_6H_4Br\text{-}p$	152–153		(51)
	139–140 (trans form)		(50)
		1 mg.*	(251)
	135		(51)
	159		(51)
	160		(51)

TABLE 19—*Continued*

Compound	Melting Point or Boiling Point °C.	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose	References
	158		(51)
	173		(51)
 $(p\text{-}CH_3OC_6H_4)_2C{=}C(CN)C_6H_4Br\text{-}p$	175–176		(51)
 $(p\text{-}CH_3OC_6H_4)_2C{=}C(CONH_2)C_6H_4Br\text{-}p$	223–225		(51)
 $(p\text{-}CH_3OC_6H_4)(o\text{-}ClC_6H_4)C{=}C(CN)C_6H_5$		0.1 mg.*	(45)
 $(C_6H_5)(p\text{-}CH_3OC_6H_4)C{=}C(CN)C_6H_4Br\text{-}p$		1 mg.*	(45)
 $(C_6H_5)(p\text{-}C_3H_7OC_6H_4)C{=}C(CN)C_6H_4Cl\text{-}p$		1 mg.*	(45)
 $(C_6H_5)(p\text{-}C_4H_9OC_6H_4)C{=}C(CN)C_6H_4Cl\text{-}p$		0.1 mg.*	(45)
			
Cis form		2 mg.* (incomplete)	(45)
Trans form		2 mg.* (incomplete)	(45)
$p\text{-}[(CH_3)_2NC_6H_4]_2C{=}C(C_6H_5)CN$	185		(50)
 $(C_6H_5)(p\text{-}C_6H_5C_6H_4)C{=}C(CN)C_6H_5$	210 184 (isomeric form)	0.1 mg.*	(47) (79) (47)
 $(C_6H_5)[p\text{-}(p\text{-}CH_3OC_6H_4)C_6H_4]C{=}C(CN)C_6H_5$			(45)
Cis form		1 mg.*	(45)
Trans form		1 mg.*	(45)

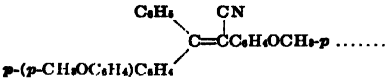
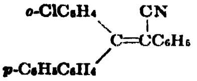
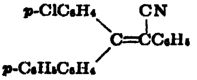
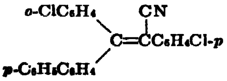
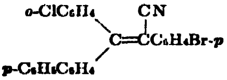
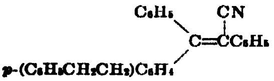
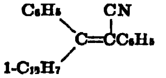
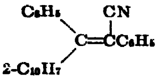
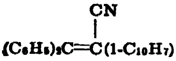
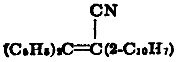
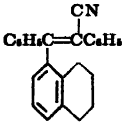
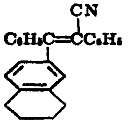
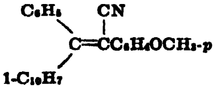
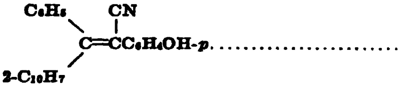
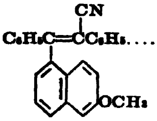
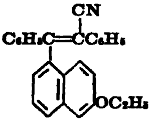
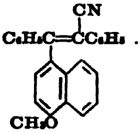
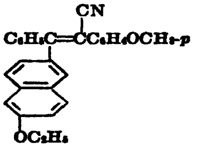
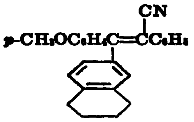
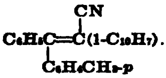
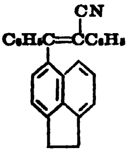
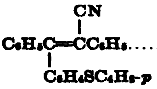
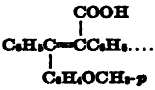
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose	References
	°C.		
 $(C_6H_5)(p\text{-}(p\text{-}CH_3OC_6H_4)C_6H_4)C{=}C(CN)C_6H_4OCH_3\text{-}p$		2 mg.* (inactive)	(45)
 $(o\text{-}ClC_6H_4)(p\text{-}C_6H_5C_6H_4)C{=}C(CN)C_6H_5$	177		(47)
 $(p\text{-}ClC_6H_4)(p\text{-}C_6H_5C_6H_4)C{=}C(CN)C_6H_5$		1 mg *	(45)
 $(o\text{-}ClC_6H_4)(p\text{-}C_6H_5C_6H_4)C{=}C(CN)C_6H_4Cl\text{-}p$		1 mg.* (inactive)	(45)
 $(o\text{-}ClC_6H_4)(p\text{-}C_6H_5C_6H_4)C{=}C(CN)C_6H_4Br\text{-}p$		2 mg.* (inactive)	(45)
 $(C_6H_5)(p\text{-}(C_6H_5CH_2CH_2)C_6H_4)C{=}C(CN)C_6H_5$	295–320/12 mm. (b.p.)		(47)
 $(C_6H_5)(1\text{-}C_{10}H_7)C{=}C(CN)C_6H_5$	176–178 (cis form)		(47, 51)
		0.1 mg.	(46)
	ca. 129–130 (trans form)		(47)
 $(C_6H_5)(2\text{-}C_{10}H_7)C{=}C(CN)C_6H_5$	180–181		(47)
		1 mg. (inactive)	(46)
 $(C_6H_5)_2C{=}C(CN)(1\text{-}C_{10}H_7)$	170–172		(51)
		1 mg.	(46)
 $(C_6H_5)_2C{=}C(CN)(2\text{-}C_{10}H_7)$	164–165		(51)
		0.1 mg.	(46)
 $C_6H_5C{=}C(CN)C_6H_5$		1 mg.*	(79)
 $C_6H_5C{=}C(CN)C_6H_5$	128–130		(47)
	140–141 (isomeric form)		(47)
 $(C_6H_5)(1\text{-}C_{10}H_7)C{=}C(CN)C_6H_4OCH_3\text{-}p$	166–167 (cis form)		(51)
		0.01 mg.	(46)
		1 mg. (8 days) ¶	(46)

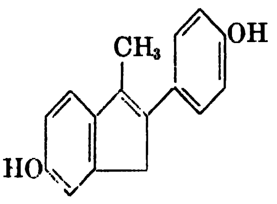
TABLE 19—*Concluded*

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose	References
	°*C.*		
 $(C_6H_5)(2\text{-}C_{10}H_7)C{=}C(CN)C_6H_4OH\text{-}p$		1 mg.*	(45)
Methyl ether	202	 0.01 mg.	(47) (46)
	160 (cis form) 146 (trans form)		(47) (47)
			
Cis form		0.1 mg. 1 mg. (36 days) ¶	(46) (46)
Trans form		0.1 mg. 1 mg. (16 days) ¶	(46) (46)
	166–167	 2 mg. (inactive)	(47) (46)
	185	 0.01 mg. 0.1 mg. (3 weeks) ¶	(47) (46) (46)
	184 171 (isomeric form)		(47) (47)
 $C_6H_5C(C_6H_4CH_3\text{-}p){=}C(CN)(1\text{-}C_{10}H_7)$	126–127	 2 mg. (inactive)	(51) (46)
	232 194 (isomeric form)	 1–2 mg.* (incomplete)	(47) (79) (47)
 $C_6H_5C(C_6H_4SC_4H_9\text{-}p){=}C(CN)C_6H_5$		10 mg.* (strongly active)	
 $C_6H_5C(C_6H_4OCH_3\text{-}p){=}C(COOH)C_6H_5$		5 mg.*	

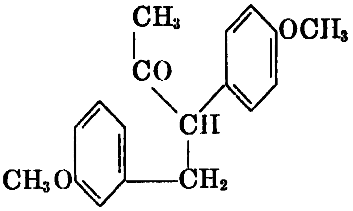
* In mice. † Orally. ¶ The period of duration of estru

structure of natural estrogens. The activity in this field has continued and highly potent estrogens have been encountered.

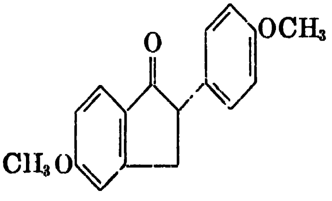
The compound 6-hydroxy-2-(*p*-hydroxyphenyl)-3-methylindene (CLXVIII), obtained by Salzer (377, 378), has presented a structural and biological problem. Salzer found a high estrogenic activity for the substance, but Adler and Hagglund (4) found it inactive at 100 micrograms and the inactivity has been confirmed by Solmssen and Wenis (466). Salzer obtained CLXVIII by cyclization of the ketone CLXIX, followed by demethylation. The cyclization was considered to proceed in the position para to the methoxyl group, but in the patent reference Salzer indicated that cyclization may occur ortho to this group. By a different route Solmssen (463) obtained two isomeric indanone intermediates melting at 96°C. and 172°C. The lower-melting isomer only could be reacted with a Grignard reagent and so was considered to be the para cyclized product (CLXX); however the evidence is not final. Silverman and Bogert (413) obtained additional evidence of the structure of Solmssen's indanone intermediates by a new synthesis. *m*-Methoxybenzyl bromide was condensed with *p*-methoxybenzyl cyanide by means of sodium amide in liquid ammonia and subsequent reaction in benzene solution, giving a 71 per cent yield of α-(*p*-methoxyphenyl)-β-(*m*-methoxyphenyl)-propionitrile (CLXXI). Hydrolysis of the nitrile gave an 85 per cent yield of the corresponding acid (CLXXII), which was cyclized to 6-methoxy-2-(*p*-methoxyphenyl)-3-indanone (CLXXIII) in 82 per cent yield by the action of stannic chloride on the acid chloride in benzene solution.



CLXVIII

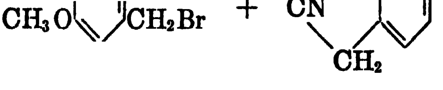


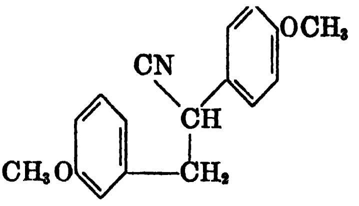
CLXIX



CLXX

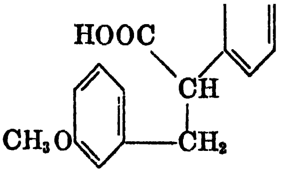
This cyclization failed with sulfuric acid, phosphorus oxychloride, or in an intramolecular Friedel–Crafts reaction using aluminum chloride.



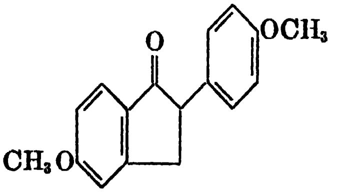


CLXXI

→

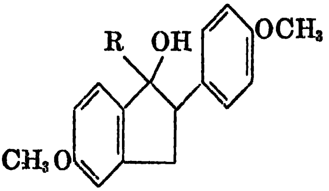


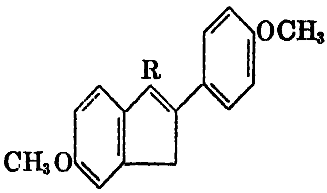
CLXXII



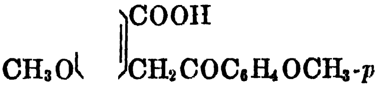
CLXXIII

→

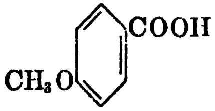




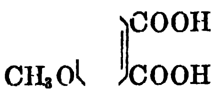
The indanone CLXXIII melted at 96–97°C. and was identical to the lower-melting compound obtained by Solmssen. The constitution of CLXXIII as the para cyclized compound was established by oxidation, 2-(*p*-methoxyphenacyl)-anisic acid (CLXXIV), anisic acid (CLXXV), and 4-methoxyphthalic acid (CLXXVI) being obtained. Conclusive evidence of the structures of these intermediates and the indenes derived from them was provided by Adler and Hagglund (4), who cyclized the symmetrical 2,3-bis(*p*-hydroxyphenyl)butadiene (CLXXVII) and its diacetate, using boron trifluoride in chloroform, and obtained CLXVIII and its diacetate.



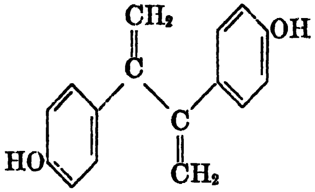
CLXXIV



CLXXV



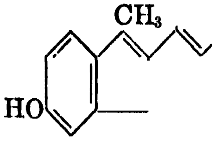
CLXXVI



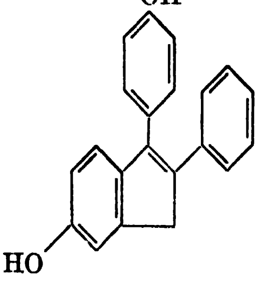
CLXXVII

By their synthesis Silverman and Bogert obtained 6-methoxy-2-(*p*-methoxyphenyl)-3-methylindene in 60 per cent yield by a Grignard reaction on CLXXIII.

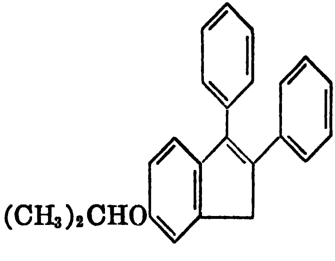
Similarly, the 3-ethyl, 3-cyclohexyl, and 3-phenyl analogs were obtained in 61, 55, and 45 per cent yields, respectively. In agreement with previous experience these compounds proved difficult to demethylate; the method used was refluxing with 48 per cent hydrobromic acid in acetic acid in a carbon dioxide atmosphere, as previously described by Solmssen (463). By this method 3-ethyl-6-hydroxy-2-(*p*-hydroxyphenyl)indene (m.p. 176–177°C.) was obtained but only in 2–3 per cent yield; it was unstable except as the diacetate. Solmssen's earlier preparation of this hydroxyindene, melting at 136°C., was apparently impure. The intermediate in the Solmssen and Silverman–Bogert synthesis was CLXXII; this was obtained by Davies and Morris (86) and by an improved procedure by Morris (294). A Perkin condensation with *p*-nitrophenylacetic acid and *m*-nitrobenzaldehyde gave *m*-nitro-α-(*p*-nitrophenyl)cinnamic acid, which on reduction with ammoniacal hydrogen sulfide or catalytically using Raney nickel gave the diamine. The diazo reaction followed by hydrogenation and methylation gave the propionic acid CLXXII, melting at 104°C. By the use of the appropriate reactants *m*-methoxy-, *m*-isopropoxy-, and *m*-benzyloxy-α-phenylcinnamic acids were obtained, and similarly the *m*-hydroxy analog was obtained. The isopropoxy and benzyloxy compounds were prepared in the hope that the indenes finally obtained might be more easily dealkylated than the methyl ethers. The cinnamic acids were hydrogenated as their sodium salts in aqueous solution, using Raney nickel; catalytic hydrogenation in alcohol failed. The *m*-methoxy and *m*-isopropoxy acids were reduced smoothly to the propionic acid, but hydrogenolysis accompanied hydrogenation of the *m*-benzyloxy acid and β-(*m*-hydroxyphenyl)-α-phenylpropionic acid was obtained. This acid was also prepared by hydrogenation of the *m*-hydroxy-α-phenylcinnamic acid. β-(*m*-Methoxyphenyl)-α-phenylpropionic acid and the *m*-isopropoxy analog were readily cyclized to the indanones by the action of stannic chloride in benzene on their acid chlorides. The *m*-benzyloxy analog was, however, debenzylated under these conditions, and phosphorus pentoxide in benzene or sulfuric acid failed to cyclize the corresponding propionic acid. The β-(*m*-hydroxyphenyl)-α-phenylpropionic acid could not be benzoylated, and although the acetate was obtained this could not be cyclized



CLXXVIII



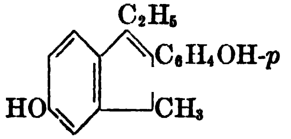
CLXXIX



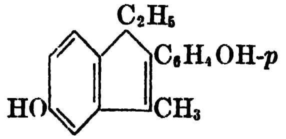
CLXXX

Attempts to dealkylate 6-methoxy-3-methyl-2-phenylindene and the 6-isopropoxy analog using hydrogen iodide–acetyl iodide and hydrogen bromide–acetic anhydride failed, as apparently water is necessary; hydrobromic acid–acetic acid did produce some dealkylation. Morris found 6-hydroxy-3-methyl-2-phenylindene (CLXXVIII) active at 5 mg.; presumably the higher dosage is due to the 2-phenyl group lacking a hydroxyl group. The indene CLXXIX is also active at the 5 mg. level, but this is a much smaller activity than that of the corresponding triphenylethylene. The related ether (CLXXX) is inactive at 5 mg. While 6-hydroxy-2-(*p*-hydroxyphenyl)-3-methylindene (CLXVIII), previously discussed, is inactive at 100 micrograms in rats, the 3-ethyl analog at 1.2 micrograms subcutaneously in mice results in 50 per cent response. These results suggest an important steric function of the 3-alkyl group.

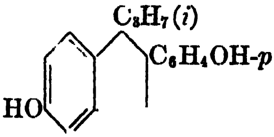
Hausmann and Wilder Smith (158) observed that losses of dienestrol occurred when dienestrol containing urines was refluxed with hydrochloric acid. These losses were accounted for when it was found that dienestrol itself, when refluxed under nitrogen with hydrochloric acid, gave good yields of a compound identified as 3-ethyl-6-hydroxy-2-(*p*-hydroxyphenyl)-1-methylindene (CLXXXI).



CLXXXI



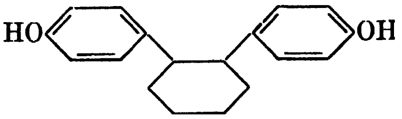
CLXXXII



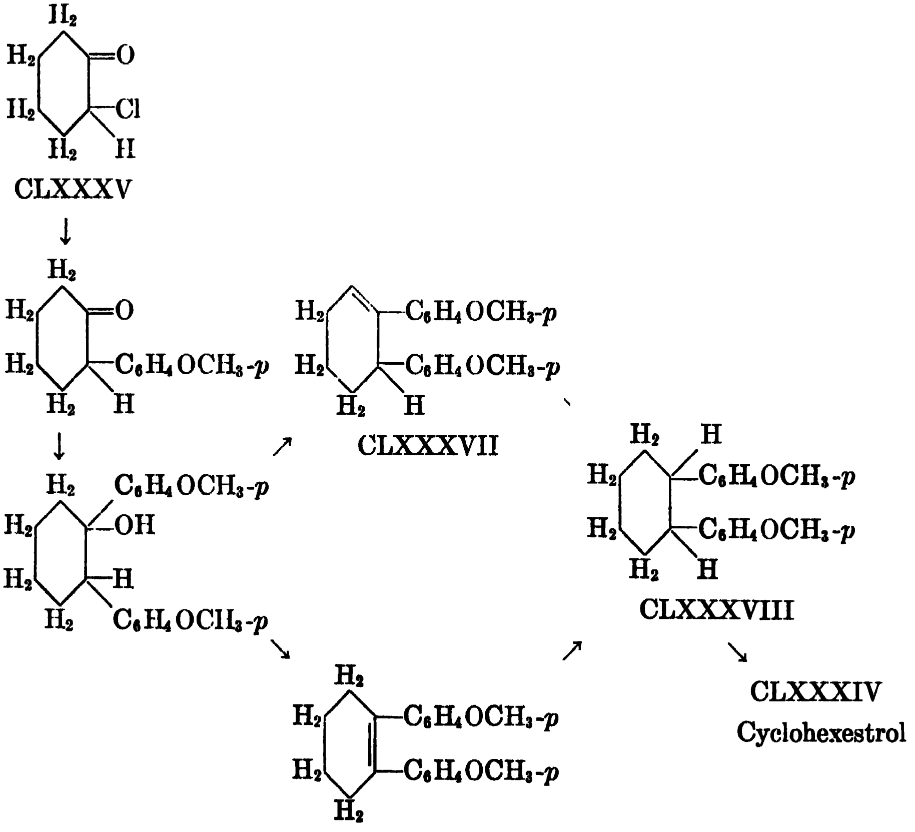
CLXXXIII

This compound, also referred to as indenestrol A, had been obtained previously in 92 per cent yield by Adler and Hagglund (4) by cyclizing dienestrol with boron trifluoride in chloroform. By the same method isodienestrol gave a 70–80 per cent yield of CLXXXI. An 82 per cent yield of the compound was obtained by Hausmann and Wilder Smith by refluxing dienestrol in acetic acid containing a drop of sulfuric acid; phosphoric acid also effected the cyclization. Adler and Hagglund (4) found that the diacetate of CLXXXI was reversibly isomerized by heating with pyridine, yielding after hydrolysis the isomer CLXXXII. Both isomers are highly active, but the biological results, which come from different sources, make it difficult to decide whether the introduction of a 1-methyl group into 3-ethyl-6-hydroxy-2-(*p*-hydroxyphenyl)indene is beneficial to estrogenic activity.

Salzer (377) hydrogenated CLXVIII to the indan but reported this hexestrol analog inactive; Solmssen (463), however, found the corresponding 3-ethylindan only slightly less active than its indene. Unlike the estrogenic indenes, the indans have satisfactory stability, a characteristic which adds further to their interest. In view of these biological results Solmssen and Wenis (466) extended the series of 3-alkylindans. The key intermediate was prepared in improved yield by a Perkin reaction between *m*-methoxybenzaldehyde and *p*-methoxyphenylacetic acid. Reduction of the cinnamic acid followed by ring closure with anhydrous hydrogen fluoride gave almost exclusively the desired indanone and in 81.4 per cent yield. Treatment with the appropriate Grignard reagent followed by dehydration with hydrochloric acid gave the 3-alkylindenes. Hydrogenation of these over 10 per cent palladium on charcoal gave the series of 3-alkyl-6-methoxy-2-(*p*-methoxyphenyl)indans; these were demethylated by 48 per cent hydrobromic acid–acetic acid. Optimum activity was found with the 3-isopropyl compound (CLXXXIII), 0.7 microgram of which gave 50 per cent response subcutaneously in rats. However, as the authors pointed out, comparison within the series and with other compounds is difficult, since only one isomer was isolated in each case and the configurations are unknown. Reaction of these indans with paraformaldehyde in alcoholic alkali gave the 1-methylene derivatives, which on reduction over Raney nickel gave a series of 3-alkyl-6-hydroxy-2-(*p*-hydroxyphenyl)-1-methylindans. In this series maximum activity was again found with the 3-isopropyl compound, although it was less active than its analog lacking the 1-methyl group. 3-Ethyl-1-methylindan required more than 16 micrograms for 50 per cent response subcutaneously in rats; Hausmann and Wilder Smith (159) obtained the same compound and reported 200 micrograms for 50 per cent re-



CLXXXIV



CLXXXV

CLXXXVII

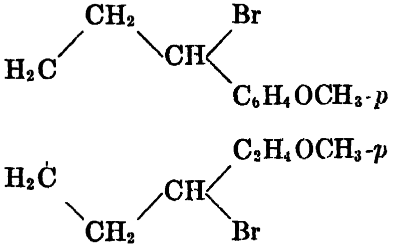
CLXXXVIII

CLXXXVI

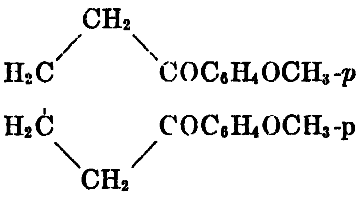
CLXXXIV
Cyclohexestrol

sponse under the same conditions. An isomer isolated by the latter workers gave 50 per cent response similarly tested at 3 micrograms, illustrating the importance of configuration in this series.

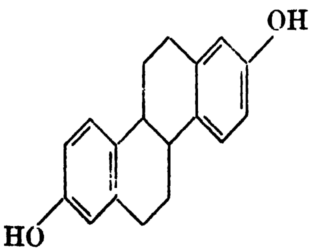
After an earlier failure by Price and Mueller (343), Mueller and May (295) succeeded in synthesizing 1,2-bis(*p*-hydroxyphenyl)cyclohexane (CLXXXIV) (cyclohexestrol), an analog of hexestrol in which the two ethyl groups are united to form a new ring. *p*-Methoxyphenylmagnesium bromide was reacted with 2-chlorocyclohexanone (CLXXXV) to give a mixture of 1,2-bis(*p*-methoxyphenyl)cyclohexene (CLXXXVI) and 2,3-bis(*p*-methoxyphenyl)cyclohexene (CLXXXVII), the former greatly in preponderance. Both halogen and carbonyl sites are attacked (305), followed by spontaneous elimination of water from the intermediate carbinol. The substituted cyclohexenes were formed when the molar ratio of 2-chlorocyclohexanone to Grignard reagent was 1:2; with a ratio of 1:1, 2-*p*-methoxyphenylcyclohexanone was the chief product. Hydrogenation of the mixture of cyclohexenes or the separate isomers over palladium on charcoal yielded 1,2-bis(*p*-methoxyphenyl)cyclohexane (CLXXXVIII), which was demethylated by alcoholic potassium hydroxide to cyclohexestrol. By relation to the hydrogenation of diethylstilbestrol, cyclohexestrol was considered to have the trans configuration. It was weakly active estrogenically. Dodds, Huang, Lawson, and Robinson (103) also prepared cyclohexestrol and found it inactive at 10 mg.; they considered it to be the cis compound. Other attempts by Mueller and May to obtain cyclohexestrol by a Wurtz or Grignard–cobaltous chloride reaction using 1,6-bis(*p*-methoxyphenyl)-1,6-dibromohexane (CLXXXIX) failed. An attempt to obtain a pinacol, as intermediate, from 1,4-bis(*p*-methoxybenzoyl)butane (CXC) failed, although an interesting polymer was produced.



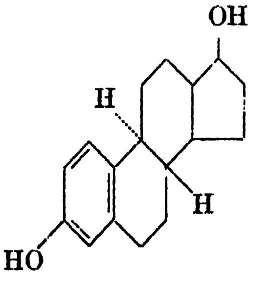
CLXXXIX



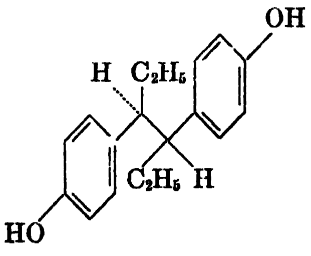
CXC



CXCI



CXCII

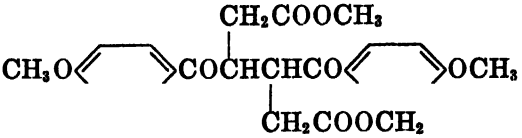


CXCIII

Nazarov and Kotlyarevskii (302) prepared 1,2-bis(*p*-hydroxyphenyl)-3-methylcyclopentane as a further variation of the union of the ethyl groups of hexestrol; it was inactive at 100 micrograms.

Wilds and Sutton (555) reëxamined the problem of the estrogenic activity of 2,8-dihydroxy-4*b*,5,6,10*b*,11,12-hexahydrochrysene, the trans form (CXCI) of which had been reported previously as active at 1000 micrograms (102).

This activity of the trans compound is surprising in view of the structural similarity to "α"-estradiol (CXCII) and hexestrol (CXCIII). Reduction of methyl *p*-methoxycinnamate with amalgamated aluminum in moist ether gave a 24 per cent and an 18 per cent yield, respectively, of the meso and racemic forms of dimethyl β,γ-dianisoyladipate (CXCIV).

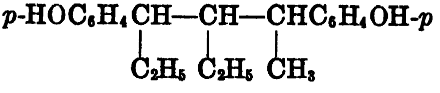


CXCIV

The meso acid chloride was cyclized in benzene with aluminum chloride and gave 88 per cent of the trans diketo compound; the cis diketo compound was obtained in 99 per cent yield by the same method. Catalytic reduction of the diketo compounds in acetic acid over palladium–charcoal gave a 90 per cent yield of the *trans*-chrysene and 70–75 per cent of the cis compound. Demethylation with 48 per cent hydrobromic acid–acetic acid gave the *trans*- and *cis*-2,8-dihydroxyhexahydrochrysenes in 94 per cent and 91 per cent yield, respectively. The trans compound gave 90 per cent response in rats subcutaneously at 500 micrograms, whereas the cis compound gave 40 per cent response at the same dosage; the trans diacetate was slightly less active than the cis diacetate. Apparently factors other than the purely structural are responsible for the activities of these isomers. The ring-closed analogs of diethylstilbestrol, hexestrol, and dienestrol are collected in table 20

VIII. DIPHENYLPROPANES AND ANALOGS

The earlier work of Blanchard, Stuart, and Tallman (25, 474) on the diphenylpropane estrogens led to the discovery of the active compound 2,4-bis(*p*-hydroxyphenyl)-3-ethylhexane (CXCV), known as benzestrol. The estrogenic ac-



$$p\text{-}HOC_6H_4\underset{\displaystyle C_2H_5}{\underset{|}{CH}}\text{—}\underset{\displaystyle C_2H_5}{\underset{|}{CH}}\text{—}\underset{\displaystyle CH_3}{\underset{|}{CH}}C_6H_4OH\text{-}p$$

CXCV

Benzestrol

tivity of this compound lies between that of estrone and "α"-estradiol, and it is claimed to be less toxic than the stilbene type of artificial estrogen. As yet, however, it has not attained extensive usage. More recently the work in this series has been extended, largely by Stuart and Tallman and their collaborators, but

TABLE 20

Ring-closed analogs of diethylstilbestrol, hexestrol, and dienestrol

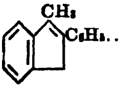
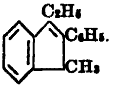
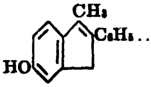
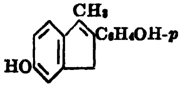
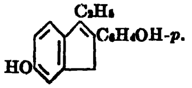
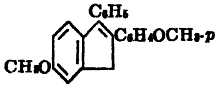
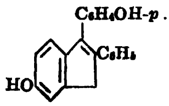
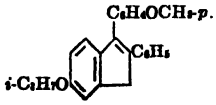
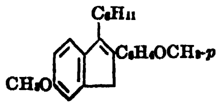
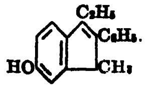
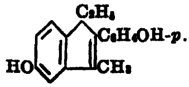
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
	76–77		(159)
	46–47		(159)
	154–155	1 mg.* (inactive) 5 mg.*	(294) (294)
Methyl ether	98–99	1 mg.* (inactive) 5 mg.*	(294) (294)
	197–198	100 (inactive)	(4)
	176–177		(413)
	115–117		(413)
	225–230	1 mg.* (inactive) 5 mg.*	(294) (294)
	145–146	5 mg.* (inactive)	(294)
	137–139		(413)
	175–176 175 175–176	3 (50%) 1	(158, 159) (4) (5, 182)
	128–129	1	(4) (5, 182)

TABLE 20—*Continued*

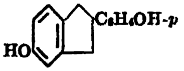
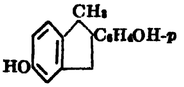
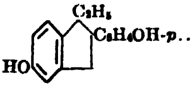
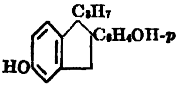
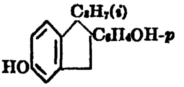
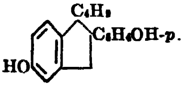
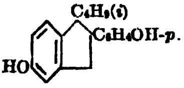
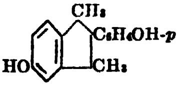
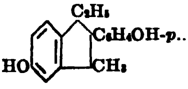
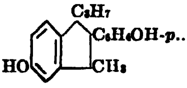
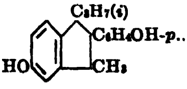
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
		>60 (50%)	(466)
	165–166 166–167	>200 (50%)	(466) (4)
	162–163	15 (50%)	(464, 466)
	145–147	2.1 (50%)	(466)
	192–194	0.7 (50%) 10† (50%)	(466) (466)
	187–188	>16 < 150 (50%)	(466)
	197–200	2.8 (50%)	(466)
	195–196	>16 (50%)	(465, 466)
	195–198 198–199 (d.) 196–197 74 (isomeric form)	>16 (50%) 200 (50%) 3 (50%)	(465, 466) (159) (4, 182) (159)
	184–185	>32 (50%)	(465, 466)
	174–181	1 (50%)	(465, 466)

TABLE 20—*Continued*

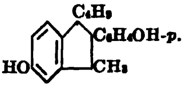
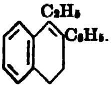
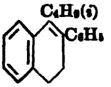
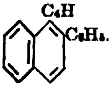
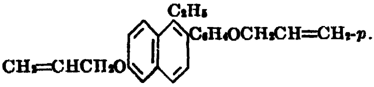
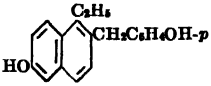
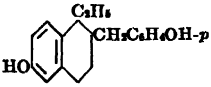
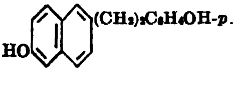
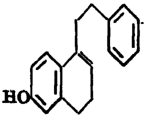
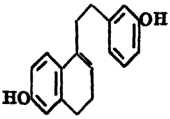
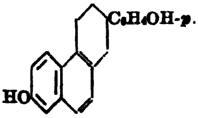
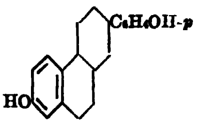
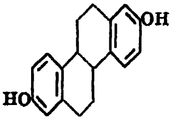
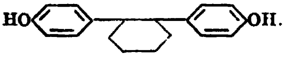
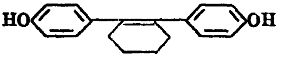
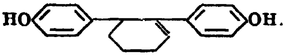
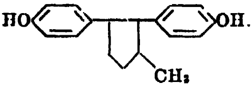
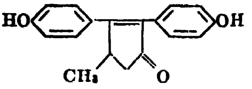
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
	174-182	>32 (50%)	(465, 466)
	222-223/34 mm. (b.p.)		(44)
	62		(44)
	57		(44)
	130-132		(413)
	164-166	0.5 mg. (inactive) 1 mg. (20%)	(219) (219)
	116-120	0.5 mg. (37%) 1 mg. (36%)	(219) (219)
	201-202	<0.001 (diethylstilbestrol = 1)	(193)
	197-198/0.8 mm. (b.p.)	1 mg (inactive)	(38)
	185-186	1-2 (weakly active)	(38)
	228.5-230.3	0.5 mg. (10%) 1 mg. (20%)	(219) (219)

TABLE 20—*Concluded*

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
	194–196	0.5 mg. (inactive) 1 mg. (10%)	(219) (219)
	269–271 (vac.) (trans form) 223.8–224.6 (cis form)	350 (60%) 500 (90%) 500 (40%)	(555) (555) (555)
Diacetate	201–202 (trans form) 213–214 (cis form)	500 (77%) 400 (80%)	(555) (555)
	177.5–179.5 176–177	200 (I.U./mg.) 10 mg. (inactive)	(295) (103)
	171–173.5	300 (I.U./mg.)	(295)
	226.6–228.6	150 (I.U./mg.)	(295)
	215–220/0.06 mm. (b.p.)	100* (inactive)	(302)
	268	100* (inactive)	(302)

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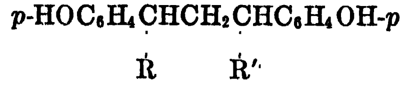
* In mice.
† Orally.

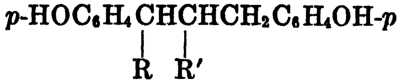
no estrogen superior to benzestrol has been encountered. The earlier work (458) showed that monoalkylated 1,3-diphenylpropanes had only low activities. Stuart, Shukis, and Tallman (472) prepared a series of dialkylated 1,3-diphenylpropanes of the type shown in formula CXCVI and observed maximum activity,



$$p\text{-}HOC_6H_4\underset{R}{CH}CH_2\underset{R'}{CH}C_6H_4OH\text{-}p \qquad p\text{-}CH_3OC_6H_4CHCH_2COC_6H_4OCH_3\text{-}p$$

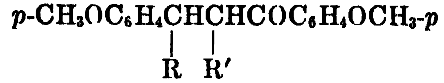
CXCVI CXCVII

of 0.2 milligram, with R = CH_3 and R″ = C_3H_7. These compounds were prepared by reacting the starting ketone (CXCVII: R = CH_3, C_2H_5, C_3H_7) with methylmagnesium iodide, followed by dehydration of the carbinol obtained by heating at 150–200°C. in a vacuum with a drop of hydrochloric acid. Yields of 80–90 per cent of the corresponding alkenes were obtained. In the same way the diethyl, ethylpropyl, and dipropyl compounds were obtained. Hydrogenation of the alkenes in acetic acid over platinum oxide and at atmospheric pressure gave practically quantitative yields of the alkanes, which were demethylated. The demethylation products were assayed without separation of isomers, a procedure which makes structural interpretation of their estrogenic activities difficult. In a second series of dialkylated 1,3-diphenylpropanes (CXCVIII)



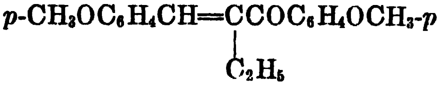
$$p\text{-HOC}_6\text{H}_4\underset{\text{R}}{\text{CH}}\underset{\text{R}'}{\text{CH}}\text{CH}_2\text{C}_6\text{H}_4\text{OH-}p$$

CXCVIII



$$p\text{-CH}_3\text{OC}_6\text{H}_4\underset{\text{R}}{\text{CH}}\underset{\text{R}'}{\text{CH}}\text{COC}_6\text{H}_4\text{OCH}_3\text{-}p$$

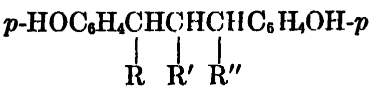
CXCIX



$$p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}{=}\underset{\text{C}_2\text{H}_5}{\text{C}}\text{COC}_6\text{H}_4\text{OCH}_3\text{-}p$$

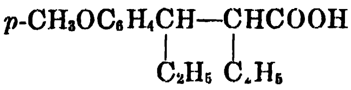
CC

the starting ketone (CC) was obtained by the condensation of anisaldehyde and *p*-methoxybutyrophenone. Reaction of this chalcone with three moles of a Grignard reagent at −10°C. gave 80 per cent yields of the ketones (CXCIX). Reaction of methylmagnesium iodide with CC failed to give a ketone of type CXCIX; instead indene-type products were obtained. The ketones (CXCIX) were separated into their two racemates and these hydrogenated over copper chromite at 230°C. and 200–250 atm. pressure; subsequent demethylation gave the racemates (CXCVIII). The B racemates (CXCVIII) (table 21) were obtained from the higher-melting racemates of the ketones. Again only the racemic products were tested biologically; the highest potency, at 0.03 milligram, was found with the racemate in which R = C_2H_5 and R′ = C_3H_7, while the racemate in which R = C_2H_5 and R′ = C_2H_5 had a closely similar activity. In a further paper (473) a series of trialkylated 1,3-diphenylpropanes (CCI) was prepared.



$$p\text{-HOC}_6\text{H}_4\underset{\text{R}}{\text{CH}}\underset{\text{R}'}{\text{CH}}\underset{\text{R}''}{\text{CH}}\text{C}_6\text{H}_4\text{OH-}p$$

CCI



$$p\text{-CH}_3\text{OC}_6\text{H}_4\underset{\text{C}_2\text{H}_5}{\text{CH}}\text{—}\underset{\text{C}_2\text{H}_5}{\text{CH}}\text{COOH}$$

CCII

The starting materials were the racemic ketones CXCIX, which by treatment with a Grignard reagent and dehydration of the carbinols as described previously gave 80 per cent yields of alkenes. Reduction using platinum oxide in ethyl alcohol and at 100°C. and 100–150 atm. pressure gave a mixture of two racemates in about equal amounts; with Raney nickel as catalyst the product consisted largely of one racemate. Demethylation yielded the racemates of CCI given in table 21; A and B, as before, refer to the racemic ketones CXCIX. When the mixture of racemates (CCI) was separated, the lower-melting, more soluble one was designated as 1 and the other as 2. When only one crystalline product was obtained, this was arbitrarily considered to be the less soluble form and was designated as 2; in other cases a mixture is assumed. Benzestrol is the B-2 race-

TABLE 21

Diphenylpropane analogs

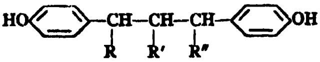
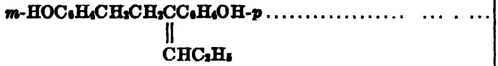
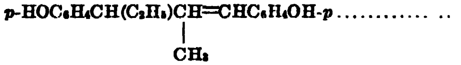
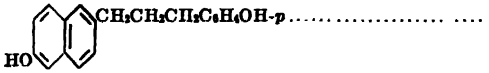
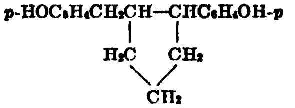
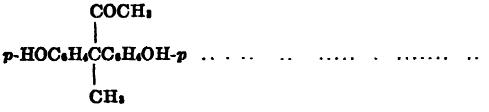
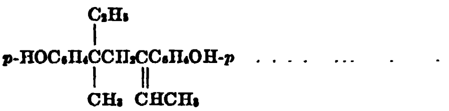
Compound 			Melting Point	Estrogenic Activity in Rats, Subcutaneously; Rat Units‡ in Milligrams Unless Indicated Otherwise	References
R	R′	R″			
			°C.		
C_2H_5	H	H	Glass		(492, 493, 495)
H	C_2H_5	H			(492, 493, 495)
CH_3	H	CH_3	144	10	(472)
CH_3	H	C_2H_5	Resin	5	(472)
CH_3	H	C_3H_7	116	0.2	(472)
C_2H_5	H	C_2H_5	86–88	1	(472)
					(492, 493, 495)
C_2H_5	H	C_3H_7	Resin	1	(472)
C_3H_7	H	C_3H_7	Resin	5	(472)
C_2H_5	CH_3	H	A 128	2.5	(472)
			B 138	5	(472)
C_2H_5	C_2H_5	H	A 52	5	(472)
					(493, 495)
			B 109	0.04	(472)
					(493, 495)
C_2H_5	C_3H_7	H	A Resin	0.25	(472)
			B Resin	0.03	(472)
C_3H_7	CH_3	H	A 84–86	7.5	(472)
			B 115	10	(472)
C_3H_7	C_2H_5	H	A 111	7.5	(472)
			B 91–93	0.2	(472)
C_3H_7	C_3H_7	H	A 57–59	10	(472)
			B Resin	0.25	(472)
C_2H_5	CF_3	CH_3	B-2 141–143	0.5	(473)
C_2H_5	CH_3	C_2H_5	A Resin	1.0	(473)
			B-2 126–127	5.0	(473)
C_2H_5	C_2H_5	C_3H_7	A-2 102	2.0	(473)
			B-2 143–144	2.0	(473)
C_2H_5	C_3H_7	C_2H_5	A Resin	0.60	(473)
			B Resin	1.0	(473)
C_2H_5	C_2H_5	C_2H_5	A-2 144	1.0	(473)
					(492, 493, 495)
			B-1 138–139	0.50	(473)
			B-2 154–155	0.10	(473)
			160–170/ 0.05 mm. (b.p.)	0.1 mg. (100%)	(103)
				0.01 mg. (inactive)	(103)
C_3H_7	C_2H_5	CH_3	A-2 132	0.40	(473)
			B-2 155	0.013	(473)
C_2H_5	C_3H_7	CH_3	A-2 68–72	0.10	(473)
			B-2 121–122	0.005	(473)
C_2H_5	C_2H_5	CH_3	A-1 Resin	0.010	(473)
			A-2 75	0.005	(473)
			B-1 144	0.035	(473, 494)
			B-2 162	0.0008	(473, 494)
			170–180/ 0.08 mm. (b.p.)	0.01 mg. (80%)	(103)

TABLE 21—*Concluded*

Compound	Melting Point	Estrogenic Activity in Rats, Subcutaneously; Rat Units‡ in Milligrams Unless Indicated Otherwise	References
	°*C.*		
o-$HOC_6H_4CH_2CH_2CH(C_2H_5)C_6H_4OH$-$p$			(493, 495)
m-$HOC_6H_4CH_2CH_2CH(C_2H_5)C_6H_4OH$-$p$			(493, 495)
p-$HOC_6H_4CH_2CH_2CH(C_3H_7)C_6H_4OH$-$o$			(493, 495)
p-$HOC_6H_4CH_2CH(C_2H_5)CH(C_2H_5)C_6H_4OH$-$o$			(493, 495)
p-$HOC_6H_4CH(C_2H_5)CH_2CH(C_2H_5)C_6H_4OH$-$o$			(493, 495)
o-$HOC_6H_4CH(CH_3)CH(C_2H_5)CH(C_2H_5)C_6H_4OH$-$p$			(493, 495)
o-$HOC_6H_4CH(C_2H_5)CH_2CH(C_2H_5)C_6H_4OH$-$o$			(493, 495)
m-$HOC_6H_4CH(C_3H_7)CH_2CH_2C_6H_4OH$-$m$	Glass	10 mg. (inactive)	(103)
m-$HOC_6H_4CH_2CH_2CH(C_3H_7)C_6H_4OH$-$p$	80–82	<0.001§	(37, 192)
 $m\text{-}HOC_6H_4CH_2CH_2\underset{\underset{CHC_2H_5}{\|}}{C}C_6H_4OH\text{-}p$	250/5 mm. (b.p)	<0.001§	(37, 192)
 $p\text{-}HOC_6H_4CH(C_2H_5)CH{=}\underset{\underset{CH_3}{\vert}}{C}HC_6H_4OH\text{-}p$	98–99	100 micrograms*	(273, 275)
	126–128	 <0.001§	(193) (37)
Diacetate	96	 <0.001§	(193) (37)
 $p\text{-}HOC_6H_4CH_2CH{-}CHC_6H_4OH\text{-}p$ (with H_2C, CH_2 and CH_2 closing a ring)			
Trans form	138–139	10 mg. (inactive)	(103)
Cis form	100.5–103	10 mg. (inactive)	(103)
$(p$-$ClC_6H_4)_2CHCCl_3$		45 mg. (inactive)	(127)
$(p$-$CH_3OC_6H_4)_2CHCCl_3$		45 mg. (inactive)	(127)
$(p$-$HOC_6H_4)_2CHCCl_3$		20 mg. 15 mg. (75%) 10 mg. (50%)	(127) (127) (127)
 $p\text{-}HOC_6H_4\overset{COCH_3}{\underset{CH_3}{C}}C_6H_4OH\text{-}p$	130-131	10 mg. (inactive)	(103)
 $p\text{-}HOC_6H_4\overset{C_2H_5}{\underset{CH_3}{C}}CH_2\underset{\underset{CHCH_3}{\|}}{C}C_6H_4OH\text{-}p$	135	0.25 microgram (= 1 unit of estrone)	(384)

* In mice.

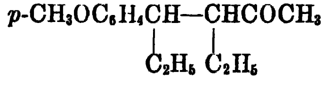
† Orally.

‡ The rat unit is defined as the minimum amount of material needed to produce complete vaginal cornification in 80 per cent of rats on single subcutaneous injection.

§ Diethylstilbestrol = 1.

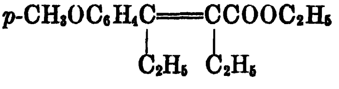
mate, m.p. 162°C. The highest activities were found with the compounds in which R = C_2H_5, R′ = C_2H_5, R″ = CH_3 and R = C_2H_5, R′ = C_3H_7 and R″ = CH_3.

Shukis and Ritter (412) substantiated the structure of benzestrol by another synthesis. The key intermediate was the known racemic α-ethyl-β-(*p*-methoxyphenyl)valeric acid (CCII), which was prepared by the condensation of anisaldehyde and methyl propyl ketone (28), followed by addition of ethylmagnesium bromide across the double bond of the unsaturated ketone. A 97 per cent yield of the ketone CCIII was obtained. The haloform reaction on this gave 21 per



$p\text{-}CH_3OC_6H_4\underset{\underset{C_2H_5}{|}}{C}H\text{—}\underset{\underset{C_2H_5}{|}}{C}HCOCH_3$

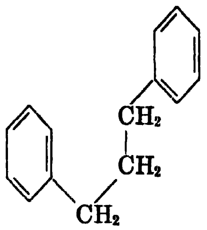
CCIII



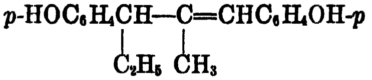
$p\text{-}CH_3OC_6H_4\underset{\underset{C_2H_5}{|}}{C}{=\!=}\underset{\underset{C_2H_5}{|}}{C}COOC_2H_5$

CCIV

cent of CCII. A second route (263) to CCII was via a Reformatsky reaction with p-methoxypropiophenone and ethyl α-bromobutyrate; an 86 per cent yield of the unsaturated ester CCIV was obtained. Reduction using platinum oxide–platinum black gave a 97 per cent yield of the dihydro compound, which on hydrolysis gave a 42 per cent yield of CCII. Conversion of racemic CCII to its acid chloride, followed by a Friedel–Crafts reaction with anisole, gave the ketone CXCIX ($R = R' = C_2H_5$); the latter with methylmagnesium iodide, dehydration, and reduction gave a 61 per cent yield of benzestrol dimethyl ether. A further procedure leading to CCII due to Rubin and coworkers (368, 369) was considered inferior. Yoshida and Akagi (559) also obtained CCII as an intermediate for use in the synthesis of benzestrol. Anisaldehyde was condensed with diethyl malonate, and ethylmagnesium iodide was added across the unsaturated ester obtained. Ethylation of the product by ethyl iodide and sodium in benzene, followed by hydrolysis and decarboxylation, gave CCII. In view of the stereoisomer problem, as indicated, it is difficult to interpret estrogenic activity in the diphenylpropane series in structural terms. However, in view of the concept of the spacing of hydrogen-bonding groups, it is probable that these compounds are adsorbed in the configuration CCV or a related configuration. The introduction



CCV



$p\text{-}HOC_6H_4\underset{\underset{C_2H_5}{|}}{C}H\text{—}\underset{\underset{CH_3}{|}}{C}{=}CHC_6H_4OH\text{-}p$

CCVI

of alkyl groups into the aliphatic portion could enhance activity by steric or adsorption means and by influencing physical properties. The polymerization of p-anol and p-anethole (459) has recently been restudied (275), and 3,5-bis(p-hydroxyphenyl)-4-methyl-4-pentene (CCVI), also called dianol, has been synthesized (273). In the synthesis a mixture of 3,5-bis(p-hydroxyphenyl)-4-methylpentenes was obtained, and this was claimed to show activity in mice subcutaneously at 0.5 microgram; dianol is active only at 100 micrograms. Metanethole, 3-ethyl-6,4′-dimethoxy-2-methyl-1-phenylindan, whose estrogenic activity has not previously been reported, was found inactive at 10 mg.

Little work on other diphenylalkanes has been reported recently, presumably since no compounds of high activity had been found previously (460, 461). However, Fisher, Keasling, and Schueler (127) investigated the activity of DDT and related compounds. 2,2′-Bis(*p*-hydroxyphenyl)-1,1,1-trichloroethane was found rather more active than its dimethyl ether or DDT. Of interest is the finding that 2,2′-bis(*p*-hydroxyphenyl)ethane is only one-seventh as active as the 1,1,1-trichloro compound. The importance of the trichloromethyl group was interpreted as increasing the hydrogen-bonding capacity of the hydroxyl groups by the operation of an inductive or direct field effect and as sterically inhibiting free rotation and so introducing rigidity into the molecule.

IX. Some Physiological Considerations

A. SOME GENERAL FACTORS AFFECTING ESTROGENIC ACTIVITY

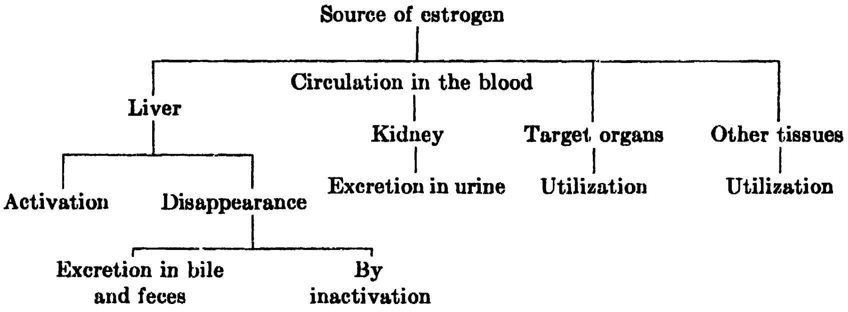
Some general factors known to affect the potency of an estrogenic substance were mentioned in the introduction. Their bearing on correlations of chemical constitution and estrogenic activity was stressed. The factor of the test animal has been exemplified previously, and this factor may lead to the frustration of an attempt to use a promising estrogen clinically. Tissue response to an estrogen is a multiple effect, and action on the vagina, the uterus, the breast, bone, and other tissues is established. The test object, therefore, is of importance in the assay of a substance, and relative activity may even be reversed by using different test objects as the criterion of activity (81). The route of administration is important, and the potency exhibited, for a particular route, depends on the rate of absorption of the estrogen (98). Oral potency is in general less than subcutaneous potency. The importance of rate of absorption is presumably due to the fact that estrogens take several days to act; easy absorption should make for ease of elimination. As indicated previously, many practical uses of this factor have been explored. Different vehicles affect potency (566); e.g., the administration of estrone with subtosan doubles its duration of action (257). Water solubility permits more rapid action of an estrogen, though a smaller physiological response will be expected. Water solubility, however, may be an asset to an estrogen which is easily inactivated. Other factors being satisfied, appropriate physicochemical properties together with chemical stability are apparently necessary for optimum activity. Unfortunately, as yet little can be said about either of these factors. For some triphenylethylene estrogens fat storage in the body after administration is established and in part at least is responsible for prolonged action (148, 503, 504). Thompson and Werner (505) found, using TACE in humans, that duration of therapy and size of dose governed the level of estrogenic material in the fat. Little information is available for other estrogens, but Koch and Heim (241, 242) demonstrated, using pigs and cows, the storage of dienestrol in fat.

The toxicity of diethylstilbestrol has been mentioned (373); it can also cause liver and kidney damage in rats (526) and dogs (528). Nicol and Helmy (306) tested several artificial and natural estrogens and found diethylstilbestrol most toxic. The compound was more toxic orally than intramuscularly. Administration of dienestrol followed by diethylstilbestrol dipropionate gave a less toxic effect than either alone. Dodds (97) considers that the potency of a substance, not its molecular features, is responsible for toxic effects. Nicol and Helmy (306) found several artificial estrogens more toxic in smaller than larger dosage and suggested the development of body resistance by overdosage. There is evidence for cooperative and antagonistic interaction between estrogen, androgen, and progestogen (80, 87, 136, 197, 245, 246, 296, 297, 408).

Heat, Höhn, and Robson (161) found that estrogen–progesterone antagonism occurred in the target organ. Arhelger and Huseby (12) found antagonism between steroid androgen and estrogen but none using diethylstilbestrol as estrogen. The results indicate competition for an intermediary or receptor; probably the hydrogen-bonding capacity of the hydroxyl groups in diethylstilbestrol make steroid androgen unable to compete. Férin (125), however, found that very large doses of testosterone acetate did inhibit the action of diethylstilbestrol in women; this supports the above conclusion.

B. INACTIVATION OF ESTROGENS

In considering estrogenic potency the possibility of metabolic inactivation is important. The pathways of estrogen in the body are indicated in the chart below:



Only a fraction of the estrogen administered is excreted (107, 210). Tissue storage cannot account for the rest (563). It was assumed that destruction or inactivation occurred in the body. Much experimental work has indicated that liver tissue is the main site of estrogen inactivation, both for natural and for artificial estrogens in rabbits, rats, guinea pigs, and dogs (22, 24, 56, 117, 147, 163, 207, 265, 339, 342, 380, 392, 564).

In humans hepatic damage has been shown to impair the inactivating ability of the liver (141, 145, 153, 381, 416, 491).

Partial hepatectomy impairs the ability of the liver to inactivate "α"-estradiol (393). Liebermann, Tagnon, and Schulman (262) recorded high inactivating ability *in vitro* to rat liver with "α"-estradiol, estrone, and estriol. The average human liver was found to be capable of metabolizing 11.5 g. of "α"-estradiol in 25 hr. (484), but there is no proved relationship for *in vivo* inactivating ability. Apparently the ability of liver to inactivate an estrogen depends on the animal;

human (514) and monkey (184) liver is inferior to rat liver. The ability of liver to inactivate an estrogen is destroyed by heating; this indicates that, at least *in vitro*, enzyme systems are involved. De Meio, Rakoff, Cantarow, and Paschkis (88) found complete inactivation of "α"-estradiol by rat liver slices under oxygen; under nitrogen or with boiled slices no inactivation occurred. Under nitrogen but in the presence of methylene blue 60 per cent inactivation occurred. It was suggested that, in part at least, a dehydrogenation mechanism was responsible for inactivation. The inactivating ability of rat liver homogenate is augmented by the addition of diphosphopyridine nucleotide (DPN) and nicotinamide (76, (88), indicating that the postulated dehydrogenation mechanism is in part linked to DPN. Heller (163) and Levy (259) found that cyanide inhibited the ability of liver to inactivate estrogen, but De Meio, Rakoff, Cantarow, and Paschkis (88) found only a limited inhibition by cyanide. This was interpreted as a limited participation of cytochrome oxidase in the inactivating process. While liver slices inactivate "α"-estradiol, liver mince was found inefficient (77), and it was concluded that cozymase participated in inactivation. Riegel and Meyer (356) attempted localization of the enzyme factors associated with inactivation by differential centrifugation of rat liver homogenate. The fractions were tested by incubation with estrogen in the presence of DPN and nicotinamide. No single fraction of nuclei, mitochondria, microsomes, or supernatant inactivated "α"-estradiol, but the microsomes and supernatant combined were as effective as homogenate; estrone behaved similarly. With diethylstilbestrol supernatant was almost as effective as homogenate; riboflavin monophosphate (RMP) alone, as well as boiled homogenate, inactivated the compound. Apparently a nonenzymatic process can inactivate diethylstilbestrol. Serchi and Principe (395) interpreted the activity of 17-ethynylestradiol and 1-ethynylcyclopentan-1-ol as indirect, arising from the liberation of acetylene from them by liver enzymes. The acetylene was postulated as destroying phenol oxidases in liver by combination with their copper component. Destruction of the functioning of phenol oxidases permits a temporary rise of estrogen in the normal circulation. Zimmerberg (562) found diethylstilbestrol incubated with rat liver slices to be partially oxidized and partially conjugated, the latter being preferred. The mechanisms were enzymatic. The problem of the nature of the metabolites remains largely to be solved, but Pearlman and De Meio (338) showed the conversion of "α"-estradiol into estrone by rat liver. There is evidence of enterohepatic circulation of estrogen with ultimate inactivation (155); during circulation small amounts of substances are lost via feces. Fishman (128) pointed out that it is not established that liver inactivation is functioning under physiological conditions regulating the metabolism of estrogens. Liver inactivation is reduced by various colloidal substances such as gelatin or methylcellulose (118, 119). Biskind and Biskind (23) found that the liver of rats on a diet deficient in vitamin B complex lost its ability to inactivate estrogens. Segaloff and Segaloff (394) concluded that thiamine and riboflavin were the important constituents of the B complex. However, Drill and Pfeiffer (109) and Jailer (211) claimed that concomitant inanition accompanying B deficiency is the factor responsible. Gyorgy (153) found that methionine or protein digests corrected B complex deficiency. Zondek and

Finkelstein (565) reported that B-deficient rats could inactivate estrone *in vivo* but that *in vitro* their liver tissue cannot. Jailer and Seaman (212) reported that the liver of rats on a 50 per cent casein diet is able to inactivate "α"-estradiol in spite of B avitaminosis or inanition. On a 15 per cent diet this ability is lost. Mentz, Odendaal, and Steyn (283) found the B vitamins essential for liver to inactivate estrogen; for optimum inactivation a certain balance between the various members of the B complex is necessary. It appears that, directly or indirectly, vitamins are associated with the capacity of the liver to inactivate estrogens (165). Folic acid is apparently not the factor associated with the vigorous capacity of the liver to inactivate estrogens *in vitro* (244). There is evidence of inactivation by blood (543).

The work described above has been done largely with steroid estrogens, although the general conclusions probably apply to many artificial estrogens. Metabolic conjugation has, however, been studied with several artificial estrogens. Wilder Smith (419) found indirectly that of estrogen administered to humans 50 per cent was excreted in urine as the monoglucuronide, 6 per cent as the sulfate ester, and less than 1 per cent in the free form. Using rabbits, Wilder Smith and Williams (421) found that 35 per cent of the diethylstilbestrol administered was excreted as the monoglucuronide; no sulfate was detected and little free estrogen. The latter fact is in agreement with the results of Mazur and Shorr (281) but in disagreement with the findings of Stroud (471). Rabbits were found to metabolize the monoglucuronide further to inactive substances. The recovery of estrogen depended on the animal; much lower recovery was found for cats. Simpson and Wilder Smith (415) attempted to elucidate the significance of estrogen conjugates and determined the activities of the monoglucuronides of diethylstilbestrol, hexestrol, and dienestrol subcutaneously and intravaginally. Activities of the order of 5–10 per cent of those of the parent substances were found, and it was concluded that their conversion to free estrogen could not explain their activities. Using diethylstilbestrol and hexestrol in rabbits, Dodgson, Garton, Stubbs, and Williams (105) found 70 per cent as monoglucuronides in urine; no sulfate was found. This was suggested as being due to the acidity of the hydroxyl groups, which is closer to that of alcoholic then phenolic hydroxyl. These authors drew attention to the different ease of hydrolysis of the monoglucuronides of diethylstilbestrol, hexestrol, and dienestrol and pointed out that only one monoglucuronide of diethylstilbestrol can exist, whereas two enantiomorphs of hexestrol can exist. Using diethylstilbestrol at the therapeutic dosage in women, Dodgson and Williams (106) obtained 35 per cent recovery as the benzylamine salt of the monoglucuronide; as indicated previously, earlier methods had been indirect. Evidence points to the liver as the site of conjugation (82, 83). Triphenylchloroethylene has been recovered from feces unchanged (215). The significance of estrogen conjugates is not yet clear, although previous discussion supports the liberation of estrogen from esters and ethers prior to biological functioning. Cohen and Marrian (74) accounted for the activity of sodium estriol glucuronide in terms of estriol content. Robson and Adler (360) found estriol glucuronide effective intravaginally, indicating a direct action. Fishman (129) considers that conjugation is a step in the utilization of estrogen by tissues and that β-glucuronidase participates in the conjugation process (128). Hanahan, Daskalakis, Edwards, and Dauben (155), however, regard conjugates as a storage form of estrogen from which free estrogen is liberated as required. In view of the low estrogenic activities of estrogen conjugates, their widespread occurrence, their stereochemistry, and their structural similarity to other esters and ethers, it does seem reasonable to view them as inactivation products.

C. ACTIVATION OF ESTROGENS

During previous discussions mention has been made of the possibility of *in vivo* modification of an administered substance with the production of an active estrogen. The concept of activation of substances and their conversion to estrogenically active metabolites has been developed largely by Emmens and his collaborators (114, 115, 116). Various compounds were given subcutaneously in oil and intravaginally in 50 per cent aqueous glycerol and the dosage needed to produce cornified smears in 50 per cent of animals determined; for each route the ratio of subcutaneous or systemic to local dosage, the S/L ratio, was found of the order of unity for some compounds and for others between 50 and 400. Compounds of the first type with an S/L ratio of unity were considered to be modified *in vivo*. Such compounds were considered unable to act directly on the vagina but were absorbed into the general circulation, metabolized, and returned to the vagina in about the same concentration as would be obtained on injection. These compounds were called proestrogens. Compounds of high S/L ratio were called true estrogens; owing to their direct action on the vagina only a small intravaginal dose was needed. The proestrogens are collected in table 22 and those considered to be true estrogens in table 23. In view of the apparent importance of hydrogen-bonding groups the proposal that compounds lacking one or more hydroxyl groups, such as α,α′-diethyl-4-hydroxystilbene, should be classified as proestrogens is understandable. Presumably *in vivo* hydroxylation occurs. However, that compounds such as α-ethyl-4,4′-dihydroxy-α-methylstilbene should be proestrogens is more difficult to understand. None of the proestrogens rigorously satisfy the structural requirements of a potent estrogen as illustrated by diethylstilbestrol, and it is possible that of an intravaginal dose only a small portion can act before delocalization of the substance occurs. Emmens examined esters of estrone, "α"-estradiol, and diethylstilbestrol and found them to be true estrogens (table 24); this surprising result was attributed to their ease of hydrolysis intravaginally. 1,1-Bis(*p*-ethoxyphenyl)-2-bromo-2-phenylethylene was found to be a proestrogen by Robson and Ansari (361); according to Emmens the dimethoxy compound is a true estrogen. 2-Chloro-1,1,2-tris(*p*-methoxyphenyl)-ethylene was found by Thompson and Werner (503) to be a proestrogen. Of interest is the report by Heat, Höhn, and Robson (161) that *trans*-androstenediol and *trans*-stilbene, classified as proestrogens by Emmens, can exert a direct estrogenic action on the atrophic rabbit.

D. THE MODE OF ACTION OF ESTROGENS

In spite of the accumulation of data in many directions, the mechanism by which a hormone acts has yet to be elucidated. It seems probable, however, that

TABLE 22

Estrogenic activities and S/L ratio for some proestrogens

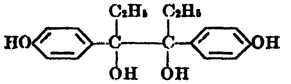
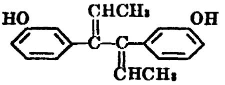
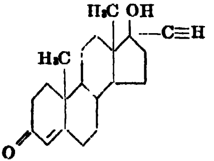
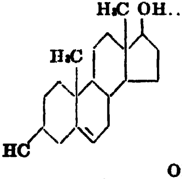
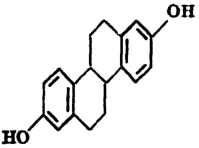
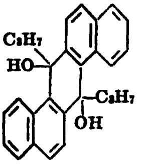
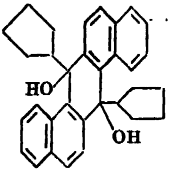
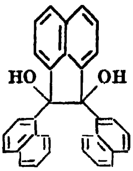
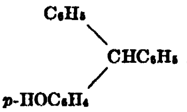
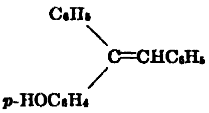
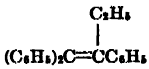
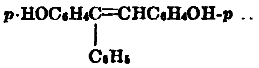
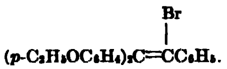
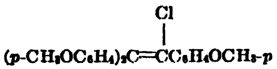
Compound	Estrogenic Activities in Mice		S/L Ratio
	Subcutaneously	Intravaginally	
	micrograms	*micrograms*	
p-$HOC_6H_4CH_2C(CH_3)_3$	40,000	>20,000	<2.0
p-$HOC_6H_4COC_2H_5$	8,000	ca. 2,000	ca. 4.0
p-$HOC_6H_4C_6H_5$	120,000	>10,000	<12.0
p-$HOC_6H_4C_6H_4OH$-p	15,000	>2,000	<7.0
p-$HOC_6H_4OC_6H_5$	30,000	>4,000	<7.0
p-$HOC_6H_4OC_6H_4OH$-p	30,000	>2,000	<15.0
$C_6H_5CH{=}CHC_6H_5$	3,200	>2,000	<1.6
p-$HOC_6H_4CH{=}CHC_6H_5$	2,000	>2,000	<1.0
p-$HOC_6H_4CH{=}CHC_6H_4OH$-p	2,200	>2,000	<1.0
p-$HOC_6H_4C(CH_3){=}CHC_6H_5$	700	>200	<3.5
p-$HOC_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_4OH$-$p$	20	>30	<0.6
p-$HOC_6H_4C(CH_3){=}C(C_2H_5)C_6H_4OH$-$p$	0.44	2.2	0.2
p-$HOC_6H_4C(i$-$C_3H_7){=}CHC_6H_4OH$-p	75	65	1.1
p-$HOC_6H_4C(C_3H_7){=}CHC_6H_4OH$-$p$	60	>60	<1.0
p-$HOC_6H_4C(C_2H_5){=}CHC_6H_4OH$-$p$	90	>80	<1.0
o-$HOC_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_4OH$-$o$	320	165	2.0
p-$HOC_6H_4CH(C_2H_5)CH_2C_6H_4OH$-$p$	650	>100	<6.5
	30	60	0.5
	300	220	1.4
	1,200	1,000	1.2
	700	800	0.9
	150	ca. 200	ca. 0.7
	18	20	0.9

TABLE 22—*Concluded*

Compound	Estrogenic Activities in Mice		S/L Ratio
	Subcutaneously	Intravaginally	
	micrograms	*micrograms*	
	490	300	1.6
	200	ca. 600	ca. 0.33
	6,000	>2,000	<3.0
$(C_6H_5)_2C{=}CHC_6H_5$	300	>200	<1.5
	20	44	0.45
$(p\text{-}HOC_6H_4)_2C{=}CHC_6H_5$	8	20	0.4
 $(C_6H_5)_2C{=}\overset{\displaystyle C_2H_5}{\overset{\vert}{C}}C_6H_5$	12	4.4	2.7
 $p\text{-}HOC_6H_4\underset{\displaystyle C_6H_5}{\underset{\vert}{C}}{=}CHC_6H_4OH\text{-}p$	15	10	1.5
 $(p\text{-}C_2H_5OC_6H_4)_2C{=}\overset{\displaystyle Br}{\overset{\vert}{C}}C_6H_5$			
 $(p\text{-}CH_3OC_6H_4)_2C{=}\overset{\displaystyle Cl}{\overset{\vert}{C}}C_6H_4OCH_3\text{-}p$			

the various identical physiological responses produced by natural and artificial estrogens proceed by the same mechanism for each hormone type. There is certainly considerable evidence showing that estrogens do affect enzyme systems both *in vitro* and *in vivo* (40, 128, 284). However, the alternative possibility of action by participation in specific transfer mechanisms through cytostructural barriers cannot be excluded (162).

TABLE 23

Estrogenic activities and S/L ratios for some true estrogens

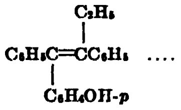
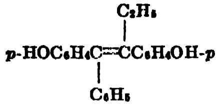
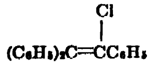
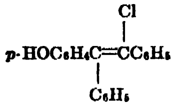
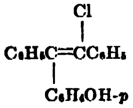
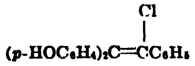
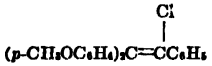
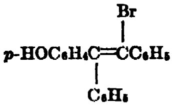
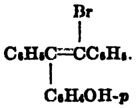
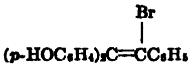
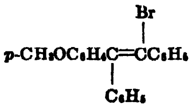
Compound	Estrogenic Activities in Mice		S/L Ratio
	Subcutaneously	Intravaginally	
	micrograms	*micrograms*	
 $C_6H_5\underset{C_6H_4OH\text{-}p}{C}=\overset{C_2H_5}{C}C_6H_5$	7.7	0.015	510
 $p\text{-}HOC_6H_4\underset{C_6H_5}{C}=\overset{C_2H_5}{C}C_6H_4OH\text{-}p$	0.9	0.00065	1,400
 $(C_6H_5)_2C=\overset{Cl}{C}C_6H_5$	77	0.89	86
 $p\text{-}HOC_6H_4\underset{C_6H_5}{C}=\overset{Cl}{C}C_6H_5$	2.3	0.0014	1,600
 $C_6H_5\underset{C_6H_4OH\text{-}p}{C}=\overset{Cl}{C}C_6H_5$	1.6	0.0013	1,200
 $(p\text{-}HOC_6H_4)_2C=\overset{Cl}{C}C_6H_5$	0.2	0.0010	200
 $(p\text{-}CH_3OC_6H_4)_2C=\overset{Cl}{C}C_6H_5$	40	1.2	33
 $p\text{-}HOC_6H_4\underset{C_6H_5}{C}=\overset{Br}{C}C_6H_5$	2.7	0.011	250
 $C_6H_5\underset{C_6H_4OH\text{-}p}{C}=\overset{Br}{C}C_6H_5$	3.0	0.010	300
 $(p\text{-}HOC_6H_4)_2C=\overset{Br}{C}C_6H_5$	0.54	0.0014	390
 $p\text{-}CH_3OC_6H_4\underset{C_6H_5}{C}=\overset{Br}{C}C_6H_5$	105	0.70	150

TABLE 23—*Concluded*

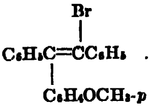
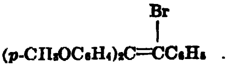
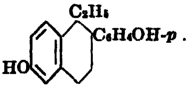
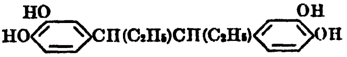
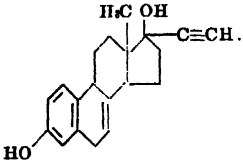
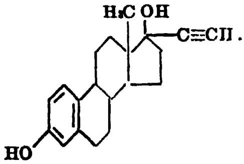
Compound	Estrogenic Activities in Mice		S/L Ratio
	Subcutaneously	Intravaginally	
	micrograms	*micrograms*	
 $C_6H_5\underset{C_6H_4OCH_3\text{-}p}{C}{=}\overset{Br}{C}C_6H_5$	100	0.49	200
 $(p\text{-}CH_3OC_6H_4)_2C{=}\overset{Br}{C}C_6H_5$	51	1.0	51
	ca. 1,000	ca. 8.0	ca. 125
$p\text{-}HOC_6H_4C(C_4H_9){=}C(C_4H_9)C_6H_4OH\text{-}p$	50	0.16	310
	12.5	0.2	63
Hexestrol (racemic)	8.9	0.025	360
$p\text{-}CH_3OC_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_4OCH_3\text{-}p$	8.0	0.02	400
$p\text{-}HOC_6H_4C(i\text{-}C_3H_7){=}C(i\text{-}C_3H_7)C_6H_4OH\text{-}p$	4.7	0.015	310
Estriol	2.0	0.001	2,000
Estrone methyl ether	0.9	0.015	60
$p\text{-}HOC_6H_4C(C_2H_5){=}C(C_3H_7)C_6H_4OH\text{-}p$	0.6	0.0035	170
ψ-Stilbestrol	0.45	0.001	450
Hexestrol (meso)	0.16	0.0009	180
Diethylstilbestrol	0.12	0.00037	320
Dienestrol	0.1	0.00058	170
Estrone	0.075	0.00029	260
	0.045	0.005	90
Estradiol	0.025	0.0005	50
	0.03	0.00025	120

TABLE 24

The effect of esterification on the S/L ratio

Compound	Estrogenic Activities in Mice		S/L Ratio
	Subcutaneously	Intravaginally	
	micrograms	*micrograms*	
Estrone	0.075	0.00029	260
Estrone butyrate	0.070	0.0003	230
Estrone caproate	0.15	0.0003	500
Estradiol	0.025	0.0005	50
Estradiol benzoate	0.08	0.0005	160
Diethylstilbestrol	0.12	0.00037	320
Diethylstilbestrol dipropionate	0.14	0.00075	190
Diethylstilbestrol dicaproate	0.45	0.0015	300
Diethylstilbestrol dipalmitate	6.0	0.0012	3,000

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REDUCTIONS INVOLVING UNIPOSITIVE MAGN[illegible]UM

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I. INTRODUCTION

Reductions effected by metals are of considerable significance. The present review is concerned with reductions brought about by the use of magnesium, but specifically with the unipositive form of this substance. Examination of the literature reveals that such reductions fall into two main categories: (*a*) those by means of unipositive magnesium anodically generated, and (*b*) reductions with magnesium–magnesium halide mixtures. In addition to a discussion of these topics, the effects on massive magnesium of a variety of organic radical-ions generated by unipositive magnesium are described.

II. REDUCTIONS WITH UNIPOSITIVE MAGNESIUM ANODICALLY GENERATED

A. Inorganic reductions in aqueous solution

There have been a number of reports in the early literature to the effect that a significant quantity of hydrogen is evolved from the anode when aqueous sodium chloride solutions are electrolyzed between magnesium electrodes (13, 16). Such behavior is indeed unusual, since the primary electrochemical process at an anode is one of oxidation, and hydrogen can be produced from water only by a process of reduction. The suggestion was made, but not proved, that unipositive magnesium was formed as an unstable intermediate, oxidation of this species to the common dipositive state by water being responsible for evolution of hydrogen (61). The initial mean valence number, V_i, for magnesium entering solution was calculated from the loss in weight of the anode and the amount of current passed through the cell, as measured by means of a copper coulometer, by the equation

$$V_i = \frac{\text{weight of copper deposited in coulometer} \times 24.32}{31.77 \times \text{weight of magnesium lost from anode}}$$

Values of V_i in the neighborhood of 1.3 were found and were stated to be independent of current density, temperature, concentration, and composition of the electrolyte (3). It was also noted that permanganate and dichromate ions were reduced at a magnesium anode in neutral solution.

What appears to be conclusive evidence for the existence of unipositive magnesium has been provided in some recent work (53). In electrolyses of aqueous sodium sulfate solutions carried out between magnesium electrodes in a divided cell, the anodic evolution of hydrogen was found to correspond satisfactorily to that expected from oxidation by water of magnesium from the measured mean valence state (ca. 1.4) to the familiar dipositive state. In the presence of a strong oxidizing agent such as chlorate ion, another reduction product in addition to hydrogen is formed in the anolyte, and the quantity of anodic hydrogen is found to be decreased. The anodic oxidation of magnesium to the unipositive state was further demonstrated by reduction of permanganate ion to manganese dioxide and silver ion to elementary silver under conditions which did not permit the oxidizing agent to come directly in contact with the anode. It should be emphasized that in the absence of electrical current the magnesium is not attacked by any of the electrolytic solutions employed.

B. Anodic reductions of organic substances in pyridine solution

In the anodic oxidation of magnesium in aqueous solutions (and of other very active metals in water, acetic acid, and liquid ammonia (14, 15, 50, 54)) evidence for the existence of lower oxidation states is obtained only when the electrolyte contains an oxidizing agent which is reduced by the species of metal of lower valence, or when the solvent itself undergoes reduction. Recently, the anodic behavior of magnesium in pyridine as solvent has been investigated. This solvent has the advantage over those cited above in that it is reduced only with great difficulty but is nevertheless a fair electrolytic medium. Therefore the behavior of dissolved oxidants can be studied without the interference of complicating solvent effects.

In the anodic oxidation of magnesium in sodium iodide–pyridine medium the metal enters solution with an initial mean valence number of two (55). However, the presence in solution of any one of a number of potential organic oxidants (for example, benzophenone, 4,4′-dimethylbenzophenone, 2′-methoxy-2,4,6-trimethylbenzophenone, benzil, nitrobenzene, azoxybenzene, azobenzene, bromobenzene, benzonitrile, benzaldehyde, and ethyl benzoate) caused the magnesium to dissolve with an initial mean valence number significantly less than two (51, 55, 56, 57, 62). Only with nitrobenzene and azoxybenzene was the magnesium attacked nonelectrolytically by the original solutions employed.

When the initial mean valence number was less than two, a reduction product(s) of the organic additive was isolated from the anolyte. Furthermore, in the majority of the cases studied, the quantity of reduction product isolated on

TABLE 1

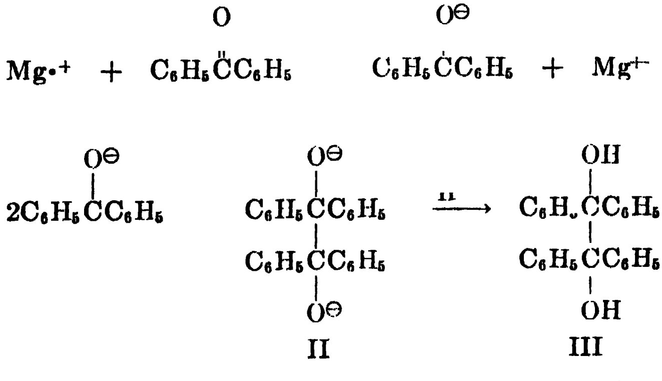
"Anodic reduction" of organic compounds by unipositive magnesium in pyridine
(Sodium iodide electrolyte)

Organic Additive	V_i	Reduction Product	Yield	Reference
			per cent	
Benzophenone	1.67–1.83	Benzopinacol	92–98	(55)
4,4'-Dimethylbenzophenone	1.54	1,1,2,2-Tetra-*p*-tolyl-1,2-ethanediol	84	(51)
Benzil	1.48	Benzoin	92	(51)
Azoxybenzene	1.05	*trans*-Azobenzene	94	(51)
2'-Methoxy-2,4,6-trimethylbenzophenone	1.90	2,2'-Dimesitoylbiphenyl*	38	(57)
trans-Azobenzene	1.57	Hydrazobenzene	87	(62)
Benzaldehyde†	1.00			(56)
Bromobenzene†	1.68			(56)
Benzonitrile†	1.72			(56)
Ethyl benzoate†	1.90			(56)
Nitrobenzene†	0.27‡			(56)

* In addition to this compound a relatively large amount of unidentified polymeric material was isolated.
† No attempt was made to isolate reduction products.
‡ This extremely low V_i is due in part to nonelectrolytic corrosion by products formed during electrolysis.

hydrolysis of the anolyte corresponded essentially quantitatively to that expected from oxidation by the organic additive of the metal from its initial mean valence state to its common +2 state. Pertinent data are given in table 1.

In view of the low V_i values found in the presence of the organic additives, and in analogy with the behavior in aqueous solution cited earlier, there appears to be little doubt that the reducing agent formed electrochemically is unipositive magnesium. Since the latter is a one-electron reductant it would appear that the first step in the reduction of any of the additives consists in the transfer of an electron from the +1 magnesium to the organic molecule. Thus in the specific case of benzophenone the electron transfer would lead to the formation of the familiar ketyl radical-ion I. Two ketyl radical-ions formed in this manner dimerize to yield the pinacolate ion II. The latter on hydrolysis gives the pinacol III. It should not be inferred from the equations shown below that the magnesium ions exist in the free (or solvated) state. They may very well be coördinated with pinacolate ions and thus drive the dimerization equilibrium to the right.



$$Mg^{\cdot+} + C_6H_5\overset{O}{\overset{\|}{C}}C_6H_5 \qquad C_6H_5\overset{O^{\ominus}}{\dot{C}}C_6H_5 + Mg^{++}$$

$$2C_6H_5\overset{O^{\ominus}}{\overset{|}{C}}C_6H_5 \qquad \begin{array}{c} O^{\ominus} \\ | \\ C_6H_5CC_6H_5 \\ | \\ C_6H_5CC_6H_5 \\ | \\ O^{\ominus} \end{array} \xrightarrow{H^+} \begin{array}{c} OH \\ | \\ C_6H_5CC_6H_5 \\ | \\ C_6H_5CC_6H_5 \\ | \\ OH \end{array}$$

II III

Similar mechanisms may be visualized for other "anodic reductions."

Incidental to the studies of "anodic reductions" the nature of the products formed at the magnesium cathode was also determined. In two cases, namely with benzophenone and 4,4′-dimethylbenzophenone, products different from those found in the anolyte were isolated from the catholyte. In both instances the corresponding benzhydrols were obtained in good yield after hydrolysis of the catholyte mixture. Cathodic reduction of benzil, *trans*-azobenzene, and azoxybenzene yielded the same products as those found in the anolyte (table 1).

III. PROPOSED MECHANISMS FOR THE ANODIC OXIDATION OF MAGNESIUM

It has been suggested (63) that in aqueous medium magnesium is oxidized anodically to a mixture of unipositive and dipositive states. Ordinarily the +1 magnesium rapidly transfers its remaining valence electron to the anode and goes into solution in the dipositive state. However, if some material (e.g., the solvent itself or some other oxidizing agent) is present which reacts with the unipositive magnesium, then the latter is oxidized to its familiar +2 state and "anodic reduction" products are obtained,—for example, hydrogen gas from reduction of the solvent in electrolyses in aqueous solution.

All the data so far accumulated on the anodic oxidation of magnesium can be equally well interpreted in terms of an alternative hypothesis: namely, that the metal is converted initially solely to the unipositive state. This primary electrochemical step is followed by the secondary processes cited above. The observed V_i value is then the result of the relative rates at which the two possible secondary competing reactions occur. This implies that the value of V_i obtained with a specific oxidant present in solution can be altered by a change in conditions which affects its relative oxidizing power, and theoretically a V_i of 1 should be attainable even under conditions where no nonelectrolytic corrosion occurs.

Although no unambiguous case in support of the second mechanism for magnesium can be cited at the present time, only this mechanism appears to be valid for the anodic oxidation of copper in aqueous medium. Thus, at 25°C. the V_i of copper in aqueous potassium chlorate is 1.58; however, with a fixed concentration of electrolyte, constant current density, and essentially constant voltage, but with increase in temperature of the anolyte, there is a progressive decrease in V_i, until at 70°C. a value of 1.00 is obtained (58). In this temperature range nonelectrolytic corrosion is negligible. Since the nature of the primary anodic process depends primarily on the applied potential and not on the temperature of the anolyte, the decrease in V_i observed with increase in temperature appears to be attributable only to an increased rate in oxidation of copper(I) by chlorate ion, and the fact that a V_i value of 1 is attained supports the hypothesis that the copper is oxidized electrochemically solely to the +1 state over the whole temperature range. It should be pointed out that when a V_i value of 1 was found, chlorate ion was reduced to chloride in quantity corresponding to oxidation of the copper(I) to the +2 state.

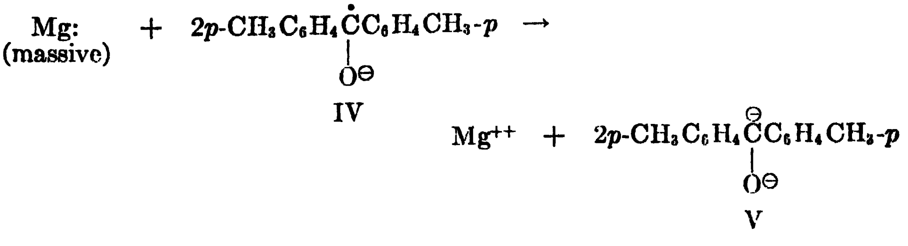
IV. CORROSION OF MASSIVE MAGNESIUM BY ORGANIC RADICAL-IONS GENERATED BY UNIPOSITIVE MAGNESIUM (48)

It is to be noted in table 1 that an abnormally low V_i value is found for magnesium when the sodium iodide–pyridine solutions contain nitrobenzene as organic additive. This fact obviously requires additional comment, since a V_i value no lower than 1 would be anticipated as a result of a strictly electrochemical process. The explanation for this anomalous behavior lies in the fact that following electrolysis the anolyte, in contrast to the behavior of a control mixture, attacked massive magnesium readily. Evidently some reduction product(s) of nitrobenzene, unlike nitrobenzene itself, is able to react with the massive magnesium anode in an oxidation–reduction process and bring some of it into solution.

Even in those cases where the V_i values lie between 1 and 2 it is entirely conceivable that the products originally produced by interaction of +1 magnesium and organic additive are capable of corroding massive magnesium, and that the V_i values in reality may be a measure of both electrochemical and nonelectrochemical effects. It should be stressed again that of the additives listed in table 1 only nitrobenzene and azoxybenzene attack magnesium in the absence of current.

The effects on massive magnesium of the products originally formed by the interaction of unipositive magnesium and a variety of organic additives in pyridine have been investigated. With every additive thus far studied evidence has been accumulated which shows that reactive products capable of attacking massive magnesium are formed. There is also strong evidence that in every case the nonelectrolytic corrosion proceeds by way of a chain reaction, with an organic radical-ion and unipositive magnesium functioning as chain carriers. The additives examined include benzophenone, 4,4′-dimethylbenzophenone, benzil, *trans*-azobenzene, and azoxybenzene.

Particularly informative examples are found in the corrosion experiments with the reactive intermediates formed from benzophenone and 4,4′-dimethylbenzophenone. In normal electrolyses with either of these ketones as additive and a magnesium anode, the corresponding pinacol is the only reduction product isolated from the anolyte after hydrolysis. However, if, after electrolysis, the anolyte solution is allowed to remain for some time in contact with the anode or with a fresh piece of magnesium, the metal is corroded and the corresponding benzhydrol, as well as the pinacol, is isolated following hydrolysis. Furthermore, the quantity of magnesium going into solution as a result of nonelectrolytic corrosion exceeds to a *considerable* extent that expected from attack on magnesium by the ketyl radical-ion (formed by interaction of the original ketone and unipositive magnesium anodically generated), in accordance with the equation shown for 4,4′-dimethylbenzophenone:



$$\underset{\text{(massive)}}{\mathrm{Mg:}} + 2p\text{-}\mathrm{CH_3C_6H_4}\overset{\bullet}{\underset{\underset{\mathrm{O}^{\ominus}}{|}}{\mathrm{C}}}\mathrm{C_6H_4CH_3}\text{-}p \rightarrow$$

IV

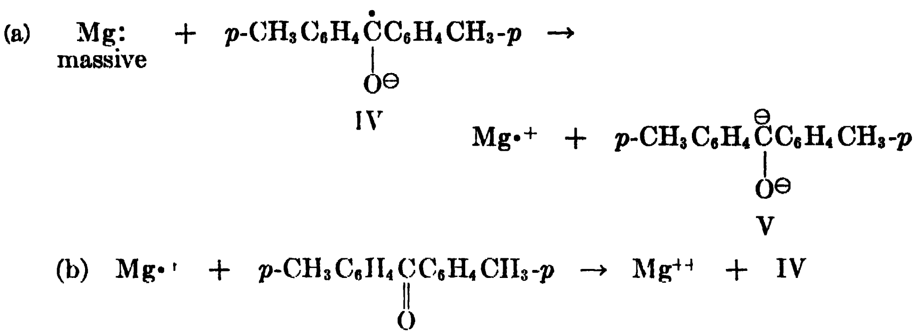
$$\mathrm{Mg}^{++} + 2p\text{-}\mathrm{CH_3C_6H_4}\overset{\ominus}{\underset{\underset{\mathrm{O}^{\ominus}}{|}}{\mathrm{C}}}\mathrm{C_6H_4CH_3}\text{-}p$$

V

The amount of ketyl radical-ion (IV) formed can be calculated from the V_i

value and coulometric data. It should be pointed out that the ketyl radical-ion originally produced undoubtedly exists in equilibrium with its dimer, but the latter serves as a reservoir for the reactive monomer.

What appears to be a valid mechanism for attack of massive magnesium by the ketyl radical-ion is the following chain of reactions:



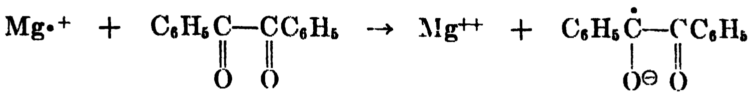
$$\text{(a)}\quad \underset{\text{massive}}{\mathrm{Mg}:} + \underset{\text{IV}}{p\text{-}\mathrm{CH_3C_6H_4}\overset{\bullet}{\underset{\mathrm{O}^{\ominus}}{\mathrm{C}}}\mathrm{C_6H_4CH_3}\text{-}p} \rightarrow \mathrm{Mg}^{\bullet +} + \underset{\text{V}}{p\text{-}\mathrm{CH_3C_6H_4}\overset{\ominus}{\underset{\mathrm{O}^{\ominus}}{\mathrm{C}}}\mathrm{C_6H_4CH_3}\text{-}p}$$

$$\text{(b)}\quad \mathrm{Mg}^{\bullet +} + p\text{-}\mathrm{CH_3C_6H_4}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{C_6H_4CH_3}\text{-}p \rightarrow \mathrm{Mg}^{++} + \text{IV}$$

Of course, V on hydrolysis affords the corresponding benzhydrol. It is only by the above sequence of reactions that the quantity of massive magnesium brought into solution after electrolysis can be explained. Although the attack of the ketyl radical-ion (IV) on the massive metal is depicted to show the formation of unipositive magnesium, the question can be raised as to whether the latter is actually formed in the free state. It is entirely conceivable that as the ketyl radical-ion abstracts an electron from one magnesium atom on the surface of the metal, a molecule of ketone accepts an electron from the metal at another point on the surface to form a new ketyl radical-ion. In any event, unless these two processes are synchronous, the active form of the metal is still essentially unipositive magnesium.

In electrolyses with benzophenone or 4,4′-dimethylbenzophenone as additive, there is evidence that the magnesium anode is *not* attacked nonelectrochemically. Thus, if the anolyte is hydrolyzed immediately after electrolysis, none of the corresponding benzhydrol is ever obtained. Since it has been shown that the ketyl radical-ion formed during electrolysis is capable of corroding massive magnesium, it is evident that the anodic process protects the metal from attack by the reactive ketyl species.

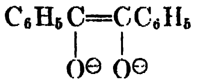
In contrast to the behavior described above for benzophenone and 4,4′-dimethylbenzophenone, in which only the pinacol is formed in simple "anodic reduction" and a mixture of pinacol and benzhydrol is formed in corrosion following electrolysis, a single product is obtained in each case under both circumstances with benzil, *trans*-azobenzene, or azoxybenzene as additive. Thus the "anodic reduction" of benzil gives, after hydrolysis, benzoin as the sole product. The latter is also obtained as the only product when the anolyte following electrolysis is permitted to stand in contact with massive magnesium. As with the ketones cited above as additives, and also in the cases of the other additives noted, the quantity of magnesium consumed as a result of nonelectrolytic attack exceeded to a considerable degree that expected merely from reaction of the metal with active intermediate produced electrochemically. There appears to be little doubt that reaction between unipositive magnesium anodically generated and benzil occurs in the following fashion:



$$\mathrm{Mg}^{\cdot+} + \mathrm{C_6H_5}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{C_6H_5} \rightarrow \mathrm{Mg}^{++} + \mathrm{C_6H_5}\underset{\underset{\mathrm{O}^{\ominus}}{|}}{\dot{\mathrm{C}}}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{C_6H_5}$$

VI

Species VI can eventually yield benzoin by one of three possible routes: (*a*) it may disproportionate in pyridine solution to form benzil and the conjugate base (VII) of benzoin;

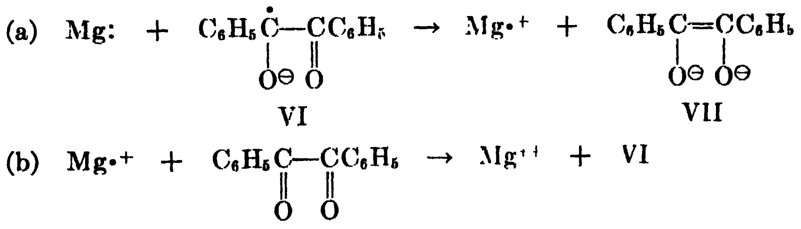


$$\mathrm{C_6H_5}\underset{\underset{\mathrm{O}^{\ominus}}{|}}{\mathrm{C}}=\underset{\underset{\mathrm{O}^{\ominus}}{|}}{\mathrm{C}}\mathrm{C_6H_5}$$

VII

(*b*) it may react further with a second $\mathrm{Mg}^{\cdot+}$ ion to give VII; or (*c*) it may disproportionate to form benzoin and benzil only after accepting a proton during hydrolysis. There is no question that VI possesses an appreciable half-life in pyridine solution, in view of the fact that the solution following electrolysis is capable of attacking massive magnesium. No other substance conceivably present in the anolyte could possibly react with massive magnesium under the experimental conditions. It is known from control experiments that benzoin itself is unreactive toward the massive metal, and attack by VII would lead, after hydrolysis, to the isolation of a reduction product of benzoin such as hydrobenzoin or desoxybenzoin.

In the light of the above discussion, nonelectrolytic corrosion can best be interpreted in terms of the chain mechanism:

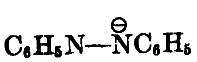


$$\text{(a)}\quad \mathrm{Mg}\colon + \mathrm{C_6H_5}\underset{\underset{\mathrm{O}^{\ominus}}{|}}{\dot{\mathrm{C}}}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{C_6H_5} \rightarrow \mathrm{Mg}^{\cdot+} + \mathrm{C_6H_5}\underset{\underset{\mathrm{O}^{\ominus}}{|}}{\mathrm{C}}=\underset{\underset{\mathrm{O}^{\ominus}}{|}}{\mathrm{C}}\mathrm{C_6H_5}$$

VI VII

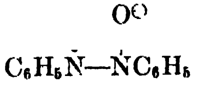
$$\text{(b)}\quad \mathrm{Mg}^{\cdot+} + \mathrm{C_6H_5}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{C_6H_5} \rightarrow \mathrm{Mg}^{++} + \mathrm{VI}$$

The "anodic reduction" of *trans*-azobenzene and of azoxybenzene yields, after hydrolysis of the anolyte, hydrazobenzene and *trans*-azobenzene, respectively. On the basis of products isolated and the extent of nonelectrolytic reaction with magnesium metal after electrolysis, the reactive intermediates formed during electrolysis are thought to have the structures VIII and IX, respectively.



$$\mathrm{C_6H_5N}-\overset{\ominus}{\mathrm{N}}\mathrm{C_6H_5}$$

VIII



$$\mathrm{C_6H_5}\dot{\mathrm{N}}-\overset{\mathrm{O}^{\ominus}}{\overset{|}{\dot{\mathrm{N}}}}\mathrm{C_6H_5}$$

IX

The effect on massive magnesium of products formed by cathodic reduction has also been examined in a limited number of cases. After electrolyses with benzil or azoxybenzene present in the pyridine solution, the catholyte (as well as the anolyte) contained a substance which attacked magnesium metal extensively. However, during the course of electrolysis the magnesium cathode suffered no loss in weight. It would appear that during electrolysis the metal cathode is protected against corrosion by the ready availability of electrons at the surface. It has been pointed out previously that the ketyl radical-ion formed in the anolyte when benzophenone or 4,4′-dimethylbenzophenone was additive did not corrode the magnesium anode during electrolysis, since no benzhydrol was obtained. Inasmuch as corrosion following electrolysis yielded no characterizable products in the anolyte other than those obtained merely on electrolysis with either benzil or azoxybenzene in the solution, it is not possible to state whether nonelectrolytic attack of the magnesium anode occurs during electrolysis in the presence of these additives.

V. REDUCTIONS WITH MAGNESIUM–MAGNESIUM IODIDE MIXTURES

No discussion of reductions by means of unipositive magnesium would be complete without consideration of the use of magnesium–magnesium halide mixtures. When magnesium and bromine, or more importantly iodine, are brought together in an appropriate organic solvent in a ratio essentially corresponding to 1 g.-atom of metal to one of halogen, the resulting mixture contains a potent reducing agent for organic substances. The same reducing power is exhibited by a mixture of metal and magnesium(II) halide. Reductions carried out with these mixtures cannot be effected by the metal alone. Therefore, the reasonable suggestion (40) has been made that the effective reducing agent is magnesium(I) halide, formed in accordance with the following equilibrium:

$$\mathrm{Mg} + \mathrm{MgX_2} \rightleftharpoons 2\mathrm{MgX}$$[1]

The literature contains many examples of the reduction by the magnesium–magnesium iodide mixture of a variety of organic compounds: e.g., ketones, aldehydes, and derivatives; carboxylic acids, esters, acid halides, and acyl peroxides; nitrobenzene and some of its reduction products. In the following sections the reduction of a limited number of representative examples of each of these classes of compounds is described. In addition, a number of interesting miscellaneous examples are given. Finally, table 2 presents a rather complete summary of the individual reductions effected.

A. Reduction of ketones and aldehydes

Pinacols are obtained by reduction of most aromatic ketones with the binary mixture magnesium + magnesium iodide, followed by hydrolysis of the reaction mixture. The reduction is ordinarily carried out in ether, benzene, or an ether–

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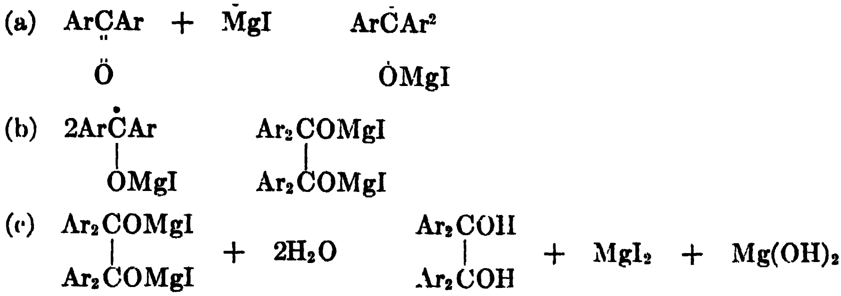
[1] The binary mixture magnesium–magnesium chloride is ineffectual as a reducing agent for organic compounds, as are mixtures of zinc–zinc halide, cadmium–cadmium halide, and aluminum–aluminum halide. However, the mixture beryllium–beryllium iodide has been shown to possess reducing power (40).

benzene mixture, frequently at elevated temperatures. It is proposed (40) that the active reducing agent, magnesium(I) iodide, reacts with a ketone to give an iodomagnesium ketyl; dimerization of the latter, followed by hydrolysis, yields the pinacol.



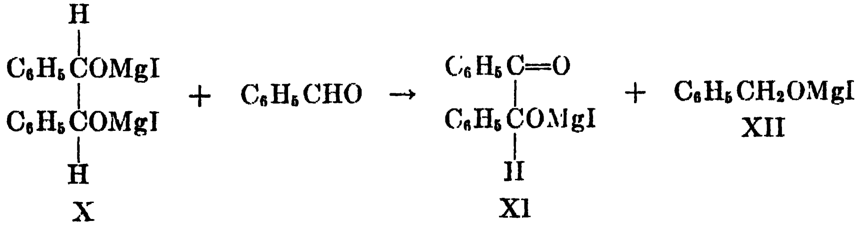
$$\text{(a)}\quad \underset{\ddot{\text{O}}}{\overset{}{\text{ArCAr}}} + \dot{\text{M}}\text{gI} \qquad \underset{\text{OMgI}}{\text{Ar}\dot{\text{C}}\text{Ar}}{}^{2}$$

$$\text{(b)}\quad 2\,\underset{\text{OMgI}}{\text{Ar}\dot{\text{C}}\text{Ar}} \qquad \begin{array}{c}\text{Ar}_2\text{COMgI}\\ |\\ \text{Ar}_2\text{COMgI}\end{array}$$

$$\text{(c)}\quad \begin{array}{c}\text{Ar}_2\text{COMgI}\\ |\\ \text{Ar}_2\text{COMgI}\end{array} + 2H_2O \qquad \begin{array}{c}\text{Ar}_2\text{COH}\\ |\\ \text{Ar}_2\text{COH}\end{array} + MgI_2 + Mg(OH)_2$$

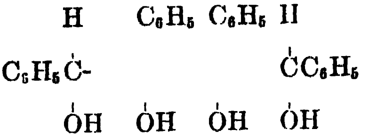
It is of interest to note that ether–benzene solutions of various aromatic ketones and magnesium–magnesium(II) iodide mixtures are highly colored, ranging from a deep red for benzophenone to an indigo blue for 4,4′-diphenylbenzophenone. Not only are these intense colors characteristic of ketyl radical-ions, but the solutions also possess other ketyl-like properties, such as extreme sensitivity to air and moisture.

Very few cases of the reduction of aromatic aldehydes by the binary mixture are on record. The reduction of benzaldehyde (43) is complex in that benzoin and benzyl alcohol are found on hydrolysis of the reaction mixture. Evidently the intermediate iodomagnesium hydrobenzoinate (X) formed in a manner analogous to that described above, for the pinacolate reacts further with benzaldehyde to produce iodomagnesium benzoinate (XI) and iodomagnesium benzylate (XII):



$$\underset{\text{X}}{\begin{array}{c}\text{H}\\ |\\ C_6H_5\text{COMgI}\\ |\\ C_6H_5\text{COMgI}\\ |\\ \text{H}\end{array}} + C_6H_5CHO \rightarrow \underset{\text{XI}}{\begin{array}{c}C_6H_5C{=}O\\ |\\ C_6H_5\text{COMgI}\\ |\\ \text{H}\end{array}} + \underset{\text{XII}}{C_6H_5CH_2OMgI}$$

The benzoinate XI can be reduced further by the binary mixture to yield, after hydrolysis, tetraphenylerythritol (XIII)



$$\begin{array}{cccc}\text{H} & C_6H_5 & C_6H_5 & \text{H}\\ C_6H_5\text{C}- & & & \text{CC}_6H_5\\ \text{OH} & \text{OH} & \text{OH} & \text{OH}\end{array}$$

XIII

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[2] Although the bond between magnesium and oxygen in this proposed intermediate is shown to be covalent, it is entirely likely that it possesses considerable ionic character.

TABLE 2

Reductions by means of the binary mixture magnesium–magnesium iodide

Substance Reduced	Product(s)	Melting Point	Yield	References
		°C.	*per cent*	
A. Ketones and aldehydes:				
Benzophenone	Benzopinacol	192–194	99.6	(40)
4-Methylbenzophenone	1,2-Diphenyl-1,2-di-*p*-tolyl-1,2-ethanediol	173–175	98	(40)
4,4′-Dimethylbenzophenone	1,1,2,2-Tetra-*p*-tolyl-1,2-ethanediol	183–184	94	(40)
4-Chlorobenzophenone	1,2-Diphenyl-1,2-di-*p*-chlorophenyl-1,2-ethanediol	172–178	94	(40)
4-Phenylbenzophenone	1,2-Diphenyl-1,2-di-*p*-biphenylyl-1,2-ethanediol	198–199	97	(40)
4,4′-Diphenylbenzophenone	1,1,2,2-Tetra-*p*-biphenylyl-1,2-ethanediol	200–203	95	(40)
9-Fluorenone	[9,9′-Bifluorene]-9,9′-diol	190–192	99	(40)
Xanthone	Xanthonepinacol	185–187	92	(40)
Anthrone	Anthronepinacol	184–185	83	(40)
4,4′-Bis(dimethylamino)benzophenone	1,1,2,2-Tetra-*p*-dimethylaminophenyl-1,2-ethanediol	196–197	53	(40)
4-Bromobenzophenone	1,2-Diphenyl-1,2-di-*p*-bromophenyl-1,2-ethanediol	178	94	(44)
3-Bromobenzophenone	1,2-Diphenyl-1,2-di-*m*-bromophenyl-1,2-ethanediol	147	85	(44)
2-Bromobenzophenone	1,2-Diphenyl-1,2 di-*o*-bromophenyl-1,2-ethanediol	160–165	Trace(a)	(44)
2-Chlorobenzophenone(b)	1,2-Diphenyl-1,2-di-*o*-chlorophenyl-1,2-ethanediol			(44)
		181	Small	(46)
		164	Small	(46)
4,4′-Dibromobenzophenone	1,1,2,2-Tetra-*p*-bromophenyl-1,2-ethanediol	179–180	94	(44)
3,3′-Dibromobenzophenone	1,1,2,2-Tetra-*m*-bromophenyl-1,2-ethanediol	152–156	40	(44)
3,4′-Dibromobenzophenone	1,2-Di-*m*-bromophenyl-1,2-di-*p*-bromophenyl-1,2-ethanediol	160–163	35	(44)
4-Chloro-4′-bromobenzophenone	1,2-Di-*p*-chlorophenyl-1,2-di-*p*-bromophenyl-1,2-ethanediol	169	60	(44)
4-Bromo-4′-phenylbenzophenone	1,2-Di-*p*-bromophenyl-1,2-di-*p*-biphenylyl-1,2-ethanediol	158–159	90	(44)
3-Bromo-4′-phenylbenzophenone	1,2-Di-*m*-bromophenyl-1,2-di-*p*-biphenylyl-1,2-ethanediol	175	64	(44)
2-Bromo-4′-phenylbenzophenone(a)				(44)
4-Methyl-4′-phenylbenzophenone	1,2-Di-*p*-tolyl-1,2-di-*p*-biphenylyl-1,2-ethanediol	180–182 175–176	93 ca. 100	(8) (11)
3-Methylbenzophenone	1,2-Diphenyl-1,2-di-*m*-tolyl-1,2-ethanediol	151–152 147–148	82 ca. 100	(8) (11)
3-Methyl-4′-phenylbenzophenone	1,2-Di-*m*-tolyl-1,2-di-*p*-biphenylyl-1,2-ethanediol	174–175	96	(8)
2-Methylbenzophenone	1,2-Diphenyl-1,2-di-*o*-tolyl-1,2-ethanediol	167 156	22 ca. 100	(8) (11)
2-Methyl-4′-phenylbenzophenone	1,2-Di-*o*-tolyl-1,2-di-*p*-biphenylyl-1,2-ethanediol	182–183	35	(8)
4-Methoxybenzophenone	1,2-Diphenyl-1,2-di-*p*-anisyl-1,2-ethanediol	173–174	45	(8)
4-Methoxy-4′-methylbenzophenone	1,2-Di-*p*-anisyl-1,2-di-*p*-tolyl-1,2-ethanediol	175–176	4	(8)
4-Methoxy-4′-phenylbenzophenone	1,2-Di-*p*-anisyl-1,2-di-*p*-biphenylyl-1,2-ethanediol	172–174	22	(8)
4-Chloro-4′-methylbenzophenone	1,2-Di-*p*-chlorophenyl-1,2-di-*p*-tolyl-1,2-ethanediol	175–176	89	(8)

TABLE 2—*Continued*

Substance Reduced	Product(s)	Melting Point	Yield	References
		°C.	*per cent*	
4-Chloro-4′-phenylbenzophenone	1,2-Di-*p*-chlorophenyl-1,2-di-*p*-biphenylyl-1,2-ethanediol	190–191	98	(8)
4-Ethoxybenzophenone	1,2-Diphenyl-1,2-di-*p*-ethoxyphenyl-1,2-ethanediol	141–142	27	(7a)
4-Ethoxy-4′-methylbenzophenone	1,2-Di-*p*-tolyl-1,2-di-*p*-ethoxyphenyl-1,2-ethanediol	168–169	22	(7a)
3-Methoxy-4′-phenylbenzophenone	1,2-Di-*p*-biphenylyl-1,2-di-*m*-methoxyphenyl-1,2-ethanediol	172–173	45	(7a)
3-Chloro-4′-phenylbenzophenone	1,2-Di-*p*-biphenylyl-1,2-di-*m*-chlorophenyl-1,2-ethanediol	174–175	77	(7a)
4-*n*-Propoxybenzophenone	1,2-Diphenyl-1,2-di-*p*-*n*-propoxyphenyl-1,2-ethanediol	146–147	62	(63)
4-*n*-Butoxybenzophenone	1,2-Diphenyl-1,2-di-*p*-*n*-butoxyphenyl-1,2-ethanediol	145–147	54	(63)
4-*n*-Amyloxybenzophenone	1,2-Diphenyl-1,2-di-*p*-*n*-amyloxyphenyl-1,2-ethanediol	119–121	42	(63)
4 Isoamyloxybenzophenone	1,2-Diphenyl-1,2-di-*p*-isoamyloxy phenyl-1,2-ethanediol	127–128	52	(63)
2,2′-Dimethylbenzophenone	2,2′-Dimethylbenzhydrol	118–119.5	ca. 25	(46)
4-Ethylbenzophenone	1,2-Diphenyl-1,2-di-*p*-ethylphenyl-1,2-ethanediol	162–163	ca. 100	(11)
4 Isopropylbenzophenone	1,2-Diphenyl-1,2-di-*p*-isopropylphenyl-1,2-ethanediol	161–162	ca. 100	(11)
4-Methyl-4′-ethylbenzophenone	1,2-Di-*p*-tolyl-1,2-di-*p* ethylphenyl-1,2-ethanediol	155–156	ca. 100	(11)
1-Naphthyl *p*-tolyl ketone	1,2-Di-*p*-tolyl-1,2-di-1-naphthyl-1,2-ethanediol	150	ca. 100	(11)
2-Methoxybenzophenone	1,2-Diphenyl-1,2-di-*o*-anisyl 1,2-ethanediol	168–169	ca. 100	(11)
3-Methoxybenzophenone	1,2-Diphenyl-1,2-di-*m*-anisyl-1,2 ethanediol	139–141	ca. 100	(11)
			20	(7a)
1-Naphthyl phenyl ketone	1,2-Diphenyl 1,2-di-1-naphthyl-1,2-ethanediol	220	46	(9)
2-Naphthyl phenyl ketone	1,2-Diphenyl-1,2-di-2-naphthyl-1,2-ethanediol	175	91	(9)
2,2′-Dibenzoylbiphenyl	9,10-Dihydro-9,10-diphenyl-9,10-phenanthrenediol	202	55	(6)
		179–180	32	
2,2′-Di-*p*-toluylbiphenyl	9,10-Dihydro-9,10-di-*p*-tolyl-9,10-phenanthrenediol	213	50	(6)
2,2′-Di-*p*-anisoylbiphenyl	9,10-Dihydro-9,10-di-*p*-anisyl-9,10-phenanthrenediol	188–190	43	(6)
1,8-Dibenzoylnaphthalene	*cis*-1,2-Diphenyl-1,2-acenaphthenediol	177.5–178	95	(12)
β-Benzopinacolone	Tetraphenylethylene	221	92	(7)
α,*β*-Epoxy-*β*-*p*-biphenylylpropiophenone(c)	1,2-Diphenyl 1,2-di-*p*-biphenylyl-1,2-ethanediol	198	46	(10)
α,*β*-Epoxy-*β*-phenylpropiophenone(c)	Benzopinacol	192–194	53	(10)
Benzil	Benzoin	135–136	95	(41)
p-Tolil	*p*-Toluoin	88–89	90	(45)
Anisil	Anisoin	113	62	(45)
4,4′-Dichlorobenzil	4,4′-Dichlorobenzoin	85–87	91	(45)
α-Naphthil	*α*-Naphthoin	138–130	91	(45)
4,4′-Diphenylbenzil	4,4′-Diphenylbenzoin	168–170	88	(45)
4-Phenylbenzil(d)	4-Phenylbenzoin	148–151	Good	(45)
Mesitil	2,2′,4,4′,6,6′-Hexamethyl-*α*,*α*′-stilbenediol	144–145	60	(21, 33)
2′,4′,6′-Trimethylchalcone	1,4-Dimesitoyl-2,3-diphenylbutane(e)			(18)

TABLE 2—*Continued*

Substance Reduced	Product(s)	Melting Point	Yield	References
		°C.	*per cent*	
2,2′,4,4′,6,6′-Hexamethylchalcone	1,4-Dimesitoyl-2,3-dimesitylbutane(e)			(18)
α-Mesityl-2,4,6-trimethylacrylophenone	1,2,5,6-Tetramesityl-1,5-hexadiene-1,6-diol	207–208	94	(20)
α-Mesityl-2,3,5,6-tetramethylacrylophenone	1,6-Diduryl-2,5-dimesityl-1,5-hexadiene-1,6-diol	196	95	(24)
2,2′,4,4′,6,6′-Hexamethylbenzophenone	2,2′,4,4′,6,6′-Hexamethylbenzhydrol	150	35	(49)
4′-Bromo-2,4,6-trimethylbenzophenone	4,4′-Dimesitoylbiphenyl	221–222	55	(19)
4′-Chloro-2,4,6-trimethylbenzophenone	4,4′-Dimesitoylbiphenyl	215–222	60	(19)
4′-Bromo-2,4,6-triethylbenzophenone	4,4′-Bis(2,4,6-triethylbenzoyl)biphenyl	148–149	13	(19)
4′-Bromo-2,4,6-triisopropylbenzophenone	4,4′-Bis(2,4,6-triisopropylbenzoyl)biphenyl	190–191	18	(19)
2′-Bromo-2,4,6-trimethylbenzophenone	2,4,6-Trimethylbenzophenone	35.5		(19)
4′-Bromo-2,3,5,6-tetramethylbenzophenone	4,4′-Diduroylbiphenyl	323–326	61	(34)
2,4,6-Trimethylbenzophenone(f)	2′-(α-Hydroxy-α-mesityl-o-tolyl)-2,4,6-trimethylbenzophenone	239–240	10	(26)
2′-Methoxy-2,4,6-trimethylbenzophenone(f)	9,10-Dimesitylphenanthrene	249–250	10	(27)
	9,10-Dihydro-9,10-dimesityl-9,10-phenanthrenediol	195–196.5	22	(31)
2,4,6-Trimethylbenzophenone and 2′-methoxy-2,4,6-trimethylbenzophenone(f)	2′-(α-Hydroxy-α-mesityl-o-tolyl)-2,4,6-trimethylbenzophenone	239–240	28	(27)
2,3,5,6-Tetramethylbenzophenone and 2′-methoxy-2,4,6-trimethylbenzophenone(f)	2′-(α-Hydroxy-α-duryl-o-tolyl)-2,4,6-trimethylbenzophenone	202–203	25	(27)
2,4,6-Trimethylbenzophenone and 2′-methoxy-2,3,5,6-tetramethylbenzophenone(f)	2′-(α-Hydroxy-α-mesityl-o-tolyl)-2,3,5,6-tetramethylbenzophenone	187–188	24	(27)
2,3,5,6-Tetramethylbenzophenone and 2′-methoxy-2,3,5,6-tetramethylbenzophenone(f)	2′ (α-Hydroxy-α-duryl-o-tolyl)-2,3,5,6-tetramethylbenzophenone	262–263	23	(27)
2′-Methoxy-2,3,5,6-tetramethylbenzophenone(f)	9,10-Diduryl-9,10-dihydro-9,10-phenanthrenediol	232	23	(31)
	9,10-Didurylphenanthrene	289.5–291.5	26	
2,2′-Diduroylbiphenyl(f)	9,10-Diduryl-9,10-dihydro-9,10-phenanthrenediol	231–232	68	(31)
2,2′-Dimesitoylbiphenyl(f)	9,10-Dihydro-9,10-dimesityl-9,10-phenanthrenediol	200.5–201.5	77	(31)
1,3-Dibenzoyl-2-phenylcyclopentane(f)	2,3,7-Triphenyl-2,3-norcamphanediol	167–168		(25)
1,2,3-Indantrione	Hydrindantin	236 (d.)	60	(59)
Benzaldehyde	Benzoin	135–136	30	(43)
	Benzyl alcohol		22	
1-Naphthaldehyde	α-Naphthoin(g)	138–139	34	(43)
	1-Naphthalenemethanol	59.5–60	26	
p-Tolualdehyde	4,4′-Dimethylbenzoin(g)	88–89	23	(43)
	p-Methylbenzyl alcohol	60	25	
Anisaldehyde	4,4′-Dimethoxybenzoin(g)	113	24	(43)
	Anisyl alcohol	24–25	30	
p-Bromobenzaldehyde	4,4′-Dibromobenzoin(g)		29	(43)
	p-Bromobenzyl alcohol	77	25	

TABLE 2—*Continued*

Substance Reduced	Product(s)	Melting Point	Yield	References
		°C	*per cent*	
p-Chlorobenzaldehyde	4,4′-Dichlorobenzoin(g)	88	24	(43)
	p-Chlorobenzyl alcohol	75	24	
2,4-Xylaldehyde	2,2′,4,4′-Tetramethylhydrobenzoin	153–154		(36)
	2,2′,4,4′-Tetramethylhydrobenzoin	129–130		
Mesitaldehyde	1,2-Dimesityl 1,2-ethanediol	214–215	20	(29)
	1,2-Dimesityl-1,2-ethanediol	160–161	54	
	1,2-Dimesitylethylene	132–133	Small	
2,4,6-Triisopropylbenzaldehyde	1,2-Bis(2,4,6-triisopropylphenyl)-1,2-ethanediol	285–286		(29)
	1,2-Bis(2,4,6-triisopropylphenyl)-1,2-ethanediol	186–187		
	1,2-Bis(2,4,6-triisopropylphenyl)-ethylene	147–148	Small	
2,3-Dimethyl-1-naphthaldehyde	1,2-Bis(2,3 dimethyl-1 naphthyl)-1,2 ethanediol	274–275.5		(29)
	1,2-Bis(2,3-dimethyl-1-naphthyl)-1,2-ethanediol	162–163.5		
B. Carboxylic acids, esters, acid halides, and acyl peroxides:				
Benzoic acid	Benzoin	135–136	30–40	(42)
	Benzil	95	4	
p-Toluic acid	4,4′-Dimethylbenzoin(h)	88 89	30	(42)
	4,4′-Dimethylbenzil(h)	102–104		
1-Naphthoic acid	*α*-Naphthoin(h)	138–139	31	(42)
	α-Naphthil(h)	189–190		
2-Naphthoic acid	*β*-Naphthoin(h)	125–126	70	(42)
	β-Naphthil(h)	157–158		
4-Biphenylcarboxylic acid	4,4′-Diphenylbenzoin(h)	228	46	(42)
	4,4′-Diphenylbenzil(h)	139–140		
Benzyl benzoate	Bibenzyl	52	70	(43)
	Benzoin	135–136	45	
Methyl benzoate	Benzoin	135–136	8	(42)
Phenyl benzoate	Phenol	43	90	(42)
Ethyl *o*-chlorobenzoate and phenylmagnesium bromide	1,2-Diphenyl-1,2-di-*o*-chlorophenyl-1,2-ethanediol(i)	163–164	5	(46)
Propionyl chloride(j)	3,4-Hexanedione		Small	(47)
Butyryl chloride(j)	4,5-Octanedione		Small	(47)
Mesitoyl chloride	2,2′,4,4′,6,6′-Hexamethyl-*α*,*α*′-stilbenediol	144–145	35	(21, 33)
	Mesitil	119–120	34	(33)
2,4,6-Triethylbenzoyl chloride	2,2′,4,4′,6,6′-Hexaethyl-*α*,*α*′-stilbenediol	154–155	30	(22,33)
	2,2′,4,4′,6,6′-Hexaethylbenzil	75–75.5	18	(22)
2,4,6-Triisopropylbenzoyl chloride	*cis*-2,2′,4,4′,6,6′-Hexaisopropylstilbenediol	175–176	37	(28)
	2,2′,4,4′,6,6′-Hexaisopropylbenzil	155–156		
4-Bromo-2,6-xyloyl chloride	4,4′-Dibromo-2,2′,6,6′-tetramethylbenzil	211.5–212.5	14	(35)
	4,4′-Dibromo-2,2′,6,6′-tetramethylbenzoin	143–144	10	
2,3,4,6-Tetramethylbenzoyl chloride	Isoduril	184–184.5		(30)
	2,2′,3,3′,4,4′,6,6′-Octamethyl-*α*,*α*′-stilbenediol			

NEW DELHI

TABLE 2—*Concluded*

Substance Reduced	Product(s)	Melting Point	Yield	References
		°C.	*per cent*	
2,3,5,6-Tetramethylbenzoyl chloride ...	Duril	250–251		(30)
	cis-2,2′,3,3′,5,5′,6,6′-Octamethyl-α,α′-stilbenediol	167–169		
2,6-Dimethylanisoyl chloride	2,2′,6,6′-Tetramethylanisil	197–198.5	38	(23)
3-Methoxymesitoyl chloride .	*cis*-2,2′,4,4′,6,6′-Hexamethyl-3,3′-dimethoxystilbenediol	138.5–139.5	55	(23)
	2,2′,4,4′,6,6′-Hexamethyl-3,3′-dimethoxybenzil	78–79	26	
2-Methyl-1-naphthoyl chloride	*cis*-Bis(2-methyl-1-naphthyl)acetylene glycol	186–188	27	(32)
	2,2′-Dimethyl-α-naphthil	160–160.5	Small	
Benzoyl peroxide	Benzoin	135–136	45	(42)
C. Nitrobenzene and some of its reduction products:				
Nitrobenzene	Aniline		Small	(38)
Nitrosobenzene .	Azobenzene(k)	68	71	(4)
Nitrosobenzene	Hydrazobenzene(k)	130	66	(4, 38)
N-Phenylhydroxylamine	Azobenzene	68		(38)
	Aniline			
Azoxybenzene	Azobenzene(l)	68	92	(4, 38)
Azoxybenzene	Hydrazobenzene(l)	130	92	(4)
4,4′ Dichloroazoxybenzene	4,4′-Dichlorohydrazobenzene	122	80	(4)
4,4′-Dimethoxyazoxybenzene	4,4′-Dimethoxyhydrazobenzene		Small	(4)
4,4′-Diphenylazoxybenzene	4,4′-Diphenylhydrazobenzene		50	(4)
	Xenylamine	53	20	
Azobenzene	Hydrazobenzene	130	89	(4)
	Aniline		6	
4,4′-Dimethylazobenzene	4,4′-Dimethylhydrazobenzene	133–134	43	(4)
	p-Toluidine	45	24	
4,4′-Dimethoxyazobenzene	*p*-Anisidine	57	20	(4)
4,4′-Diphenylazobenzene	4,4′-Diphenylhydrazobenzene		32	(4)
	Xenylamine	53	32	
D. Miscellaneous compounds:				
Di-*p*-anisylthioketone	Tetra-*p*-anisylethylene sulfide	210 (d.)	37	(60)
Benzalaniline .	α,α′-Dianilinobibenzyl	137–139	100	(5)
Benzophenone anil	*N*-Phenylbenzohydrylamine	57–58		(5)
Fluorenone anil	*N*-Phenyl-9-fluorylamine	121–123	83	(5)
Benzil monoanil	α-Anilino α-phenylacetophenone	97–98	80	(5)
Diphenylmethane	1,1,2,2-Tetraphenylethane	211	Small	(39)
N,*N*-Diphenylhydroxylamine..	Diphenylamine	54	18	(38)
5,12-Dihydro-5,12-diphenyl-5,12-naphthacenediol(m)	5,12-Diphenylnaphthacene	207–208	73	(1)
p-(1-Chloropropyl)anisole(j)	3,4-Bis(*p*-hydroxyphenyl)hexane	188	100	(2)
Hexadecylmagnesium iodide . ..	Dotriacontane	71–72	70	(52)

(a) An appreciable amount of the original ketone was "destroyed through loss of nucleus bromine."

(b) This compound behaves like its bromo analog.

(c) The reducing mixture contained magnesium, magnesium bromide, and phenylmagnesium bromide.

(d) Magnesium–magnesium bromide proved to be a more satisfactory reducing mixture than magnesium–magnesium iodide. It was not established whether the product was 4- or 4′-phenylbenzoin.

(e) Two stereoisomeric forms were isolated.

(f) The solvent employed was a mixture of toluene and *n*-butyl ether.

(g) The product was isolated as the corresponding benzil by oxidation, after reduction with the binary mixture.

(h) Actually, the crude reduction product consisting of both the benzoin and benzil was oxidized to the corresponding benzil. Yields reported are in terms of the benzil.

(i) Evidently phenylmagnesium bromide first reacts with ethyl *o*-chlorobenzoate to give 2-chlorobenzophenone, which is then reduced to the pinacol by the binary mixture. A large amount of diphenyl-*o*-chlorophenylcarbinol is also formed.

(j) Ethyl ether was employed as solvent.

(k) Azobenzene is obtained from the reaction of nitrobenzene, magnesium, and magnesium(II) iodide in equimolar quantities; with an excess of the binary mixture hydrazobenzene is the product.

(l) An equimolar mixture of azoxybenzene, magnesium, and magnesium(II) iodide gave azobenzene after hydrolysis; with an excess of magnesium–magnesium iodide hydrazobenzene is produced.

(m) The reducing agent was magnesium–magnesium bromide mixture.

and a polymer. Sterically hindered benzaldehydes, such as mesitaldehyde, give normal bimolecular reduction products (29).

B. Reduction of carboxylic acids, esters, acid halides, and acyl peroxides

Aromatic acids in ether–benzene solution react with the binary mixture in two stages (42): (*a*) quantitative conversion of the acid to the iodomagnesium salt, ArCOOMgI, with the evolution of hydrogen; and (*b*) bimolecular reduction of the salt to yield benzil and the further reduction product

$$ArC(OMgI){=}C(OMgI)Ar$$

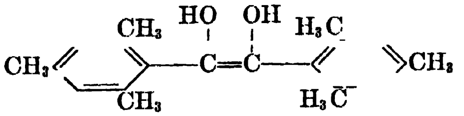
the latter giving the appropriate benzoin on hydrolysis.

Alkyl esters of aromatic acids, such as benzyl benzoate or methyl benzoate, in ether–benzene solution in the presence of the binary mixture are first cleaved by magnesium(II) iodide:

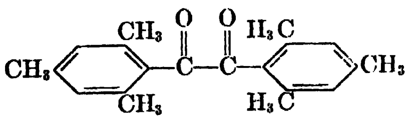
$$ArCOOCH_2R + MgI_2 \rightleftharpoons ArCOOMgI + RCH_2I$$

The iodomagnesium salt formed is then reduced by the binary mixture in the manner described above (42). The action of the binary mixture on one aryl ester, phenyl benzoate, has been reported (42). This compound gives iodomagnesium phenoxide, C_6H_5OMgI, and a resin, undoubtedly arising from reaction of the binary mixture with benzoyl iodide, formed in the cleavage Phenol is the only identifiable product isolated on hydrolysis.

The reducing action of the binary mixture has been utilized for the preparation of α-diketones from aliphatic acid chlorides (47). In this manner 3,4-hexanedione and 4,5-octanedione were prepared from propionyl chloride and butyryl chloride, respectively. A number of hindered acid chlorides have been reduced. For example, mesitoyl chloride is converted, after reduction and hydrolysis, to a mixture of 2,2′,4,4′,6,6′-hexamethyl-α,α′-stilbenediol (XIV) and mesitil (XV) (21, 33). Other examples of the reduction of hindered acid chlorides are listed in table 2.



XIV



XV

Benzoyl peroxide reacts vigorously with magnesium–magnesium iodide mixtures to form the iodomagnesium salt, $C_6H_5COOMgI$, which, as with benzoic acid, yields benzoin on further reduction and hydrolysis (42)

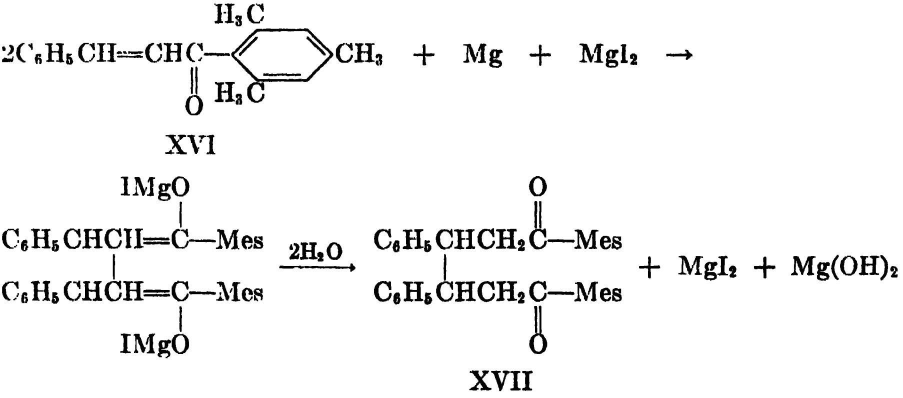
C. *Reduction of nitrobenzene and some of its reduction products*

It has been reported (38) that nitrobenzene undergoes slow reduction by the binary mixture to give, after hydrolysis, a poor yield of aniline. Azobenzene is obtained as the major product from the reaction of nitrosobenzene, magnesium, and magnesium(II) iodide in equimolar quantities (4). Nitrosobenzene is reduced by an excess of magnesium–magnesium iodide mixture principally to the iodomagnesium salt of hydrazobenzene, which upon hydrolysis produces hydrazobenzene (4, 38). The latter may also be produced directly from azobenzene, aniline being also formed to a small degree (4, 38). An equimolar mixture of azoxybenzene, magnesium, and magnesium iodide yields, after hydrolysis, azobenzene (4, 38). Reduction of *N*-phenylhydroxylamine gives azobenzene and aniline (38). Although no mention was made of the isolation of hydrazobenzene in this reaction, it appears evident that this product must also have been formed. It is of interest that when just sufficient reducing agent is employed to convert nitrosobenzene to azoxybenzene, the latter is not formed, but rather the product consists of a mixture of azobenzene and unchanged nitrosobenzene (4).

Three examples have been reported in which substituted azobenzenes have been subjected to reduction by the binary mixture. 4,4′-Dimethylazobenzene, 4,4′-dimethoxyazobenzene, and 4,4′-diphenylazobenzene are converted in part to the corresponding hydrazobenzenes, but reduction to the respective anilines occurs to a considerably greater extent in these cases than with azobenzene itself (4).

D. *Conjugate bimolecular reductions*

In addition to the simple bimolecular reductions of carbonyl compounds already described, the literature contains numerous examples of conjugate bimolecular reductions by the binary mixture (18). The latter fall into two main categories: those in which there is simply union of two molecules of the carbonyl compound and those in which union is accompanied by elimination of a small stable anion, such as methoxide or halide. A number of illustrative examples of such reductions are discussed.

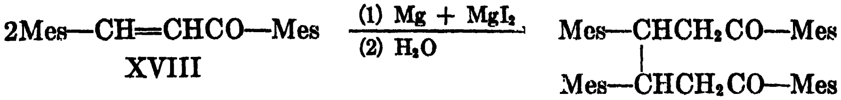


XVI

XVII

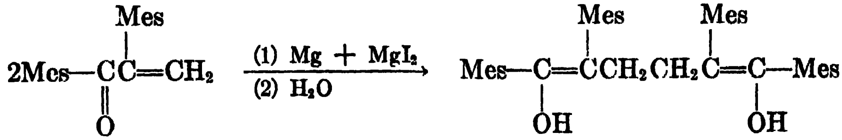
The reduction of 2′,4′,6′-trimethylchalcone (XVI) gives, after hydrolysis, two isomeric forms of the diketone XVII (18).

It is of interest that 2,2′,4,4′,6,6′-hexamethylchalcone (XVIII) behaves similarly, coupling occurring at a highly hindered carbon atom (18).



$$\underset{\text{XVIII}}{\text{2Mes—CH=CHCO—Mes}} \xrightarrow[\text{(2) H}_2\text{O}]{\text{(1) Mg + MgI}_2} \begin{array}{l}\text{Mes—CHCH}_2\text{CO—Mes}\\ \qquad\;| \\ \text{Mes—CHCH}_2\text{CO—Mes}\end{array}$$

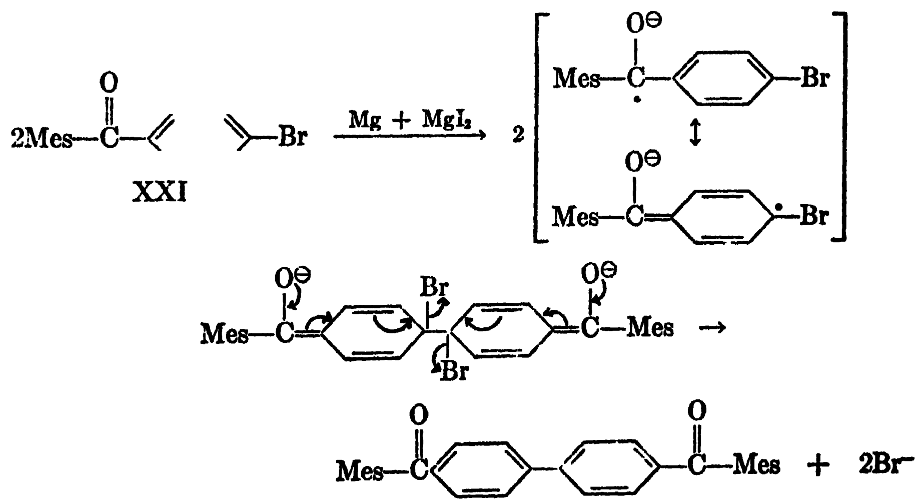
Evidence that coupling occurs through the formation of a dienolate is provided by the behavior of α-mesityl-2,4,6-trimethylacrylophenone (XIX) toward the binary mixture. After hydrolysis, the dienol XX is isolable (20).



$$2\text{Mes}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\overset{\overset{\text{Mes}}{|}}{\text{C}}=\text{CH}_2 \xrightarrow[\text{(2) H}_2\text{O}]{\text{(1) Mg + MgI}_2} \text{Mes}-\underset{\underset{\text{OH}}{|}}{\text{C}}=\overset{\overset{\text{Mes}}{|}}{\text{C}}\text{CH}_2\text{CH}_2\overset{\overset{\text{Mes}}{|}}{\text{C}}=\underset{\underset{\text{OH}}{|}}{\text{C}}-\text{Mes}$$

XIX XX

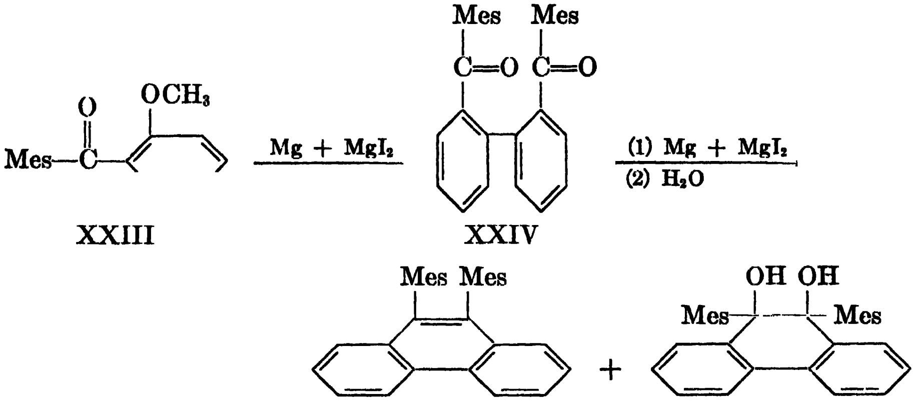
The effect of the binary mixture on highly hindered diaryl ketones sterically incapable of forming pinacols has been investigated. Conjugate bimolecular reduction of 4′-bromo-2,4,6-trimethylbenzophenone (XXI) occurs with the elimination of bromide ion and the production of 4,4′-dimesitoylbiphenyl (XXII) (34).



XXI

XXII

Another example of coupling with the elimination of an anion, specifically the methoxide ion, is found in the reduction of 2′-methoxy-2,4,6-trimethylbenzophenone (XXIII) (27, 31).



XXIII XXIV

Although the proposal was made that 2,2′-dimesitoylbiphenyl (XXIV) is formed as an intermediate in the reaction, this compound was not isolated. It is worth noting that XXIV is obtained in the reduction of XXIII by means of unipositive magnesium anodically generated (table 1).

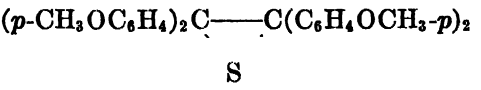
E. Reduction of miscellaneous compounds

Isolated examples of the reduction of a wide variety of functional groups not falling in any of the categories previously noted have also been described. A number of such reductions are cited below.

Aromatic thioketones are transformed by the magnesium–magnesium iodide mixture into the corresponding ethylene sulfides. For example, di-*p*-anisylthioketone (XXV) yields tetra-*p*-anisylethylene sulfide (XXVI) (60).

$(p\text{-}CH_3OC_6H_4)_2C{=}S$

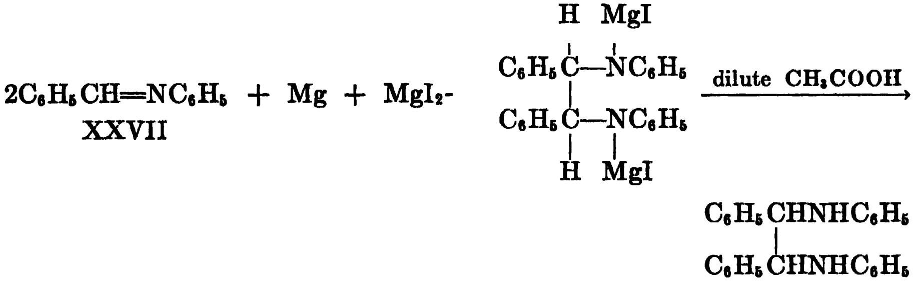
XXV



$$(p\text{-}CH_3OC_6H_4)_2\underset{\diagdown\ S\ \diagup}{C\text{———}C}(C_6H_4OCH_3\text{-}p)_2$$

XXVI

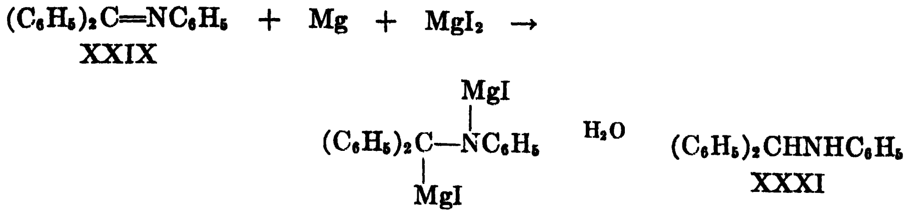
Since magnesium–magnesium iodide adds to the azo and carbonyl groups, it is of interest to compare the behavior of the azomethine group toward this mixture. Two different effects have been observed. Whereas benzalaniline (XXVII) gives, after hydrolysis, α,α'-dianilinobibenzyl (XXVIII), benzophenone anil (XXIX) and benzil monoanil (XXX) give *N*-phenylbenzohydrylamine (XXXI) and α-anilino-α-phenylacetophenone (XXXII), respectively (5).



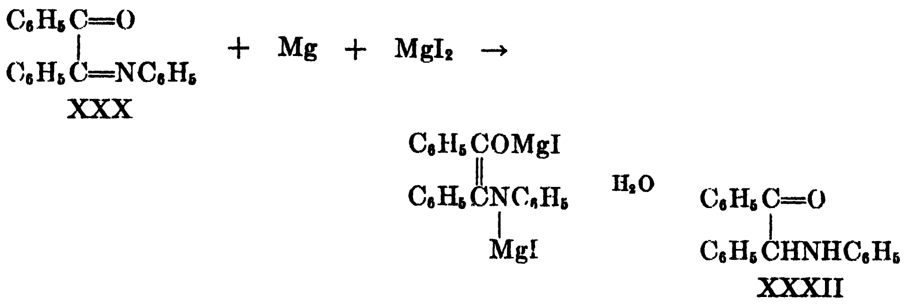
$$2C_6H_5CH{=}NC_6H_5 + Mg + MgI_2 \rightarrow \begin{array}{l} \quad H \quad MgI \\ C_6H_5C\text{—}NC_6H_5 \\ C_6H_5C\text{—}NC_6H_5 \\ \quad H \quad MgI \end{array} \xrightarrow{\text{dilute } CH_3COOH} \begin{array}{l} C_6H_5CHNHC_6H_5 \\ C_6H_5CHNHC_6H_5 \end{array}$$

XXVII

XXVIII



$$\underset{\text{XXIX}}{(C_6H_5)_2C{=}NC_6H_5} + Mg + MgI_2 \rightarrow (C_6H_5)_2\underset{\displaystyle MgI}{C}{-}\overset{\displaystyle MgI}{N}C_6H_5 \xrightarrow{H_2O} \underset{\text{XXXI}}{(C_6H_5)_2CHNHC_6H_5}$$



$$\underset{\text{XXX}}{\begin{array}{l} C_6H_5C{=}O \\ \ \ | \\ C_6H_5C{=}NC_6H_5 \end{array}} + Mg + MgI_2 \rightarrow \begin{array}{l} C_6H_5COMgI \\ \ \ \| \\ C_6H_5CNC_6H_5 \\ \ \ \ \ | \\ \ \ \ \ MgI \end{array} \xrightarrow{H_2O} \underset{\text{XXXII}}{\begin{array}{l} C_6H_5C{=}O \\ \ \ | \\ C_6H_5CHNHC_6H_5 \end{array}}$$

In contrast to the behavior of benzophenone anil (XXIX) toward the binary mixture, attempted reduction of the ethylenic analog, 1,1-diphenylethylene, was unsuccessful (37). Only two other attempts have been made to effect reaction of magnesium–magnesium iodide with hydrocarbons. No evidence of reduction was found with triphenylmethane, but a very small quantity of 1,1,2,2-tetraphenylethane was obtained from diphenylmethane (39).

Reduction of *N*,*N*-diphenylhydroxylamine yields diphenylamine (38).

Reaction of the binary mixture with *o*- and *p*-quinones has been studied (17). The products are the expected quinols.

5,12-Diphenylnaphthacene is obtained by the action of magnesium–magnesium bromide mixture on 5,12-dihydro-5,12-diphenyl-5,12-naphthacenediol (1).

F. Summary of reductions with the magnesium–magnesium iodide mixture

The numerous reductions effected by means of the binary mixture magnesium–magnesium iodide are listed in table 2. The solvent employed in each case, unless otherwise noted, was a mixture of ether and benzene. In many of the reductions cited the products can exist in two or more stereoisomeric forms. Appropriate notation has been made when isomers have been identified by the authors of the original articles.

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THE PHOTOLUMINESCENCE AND ASSOCIATED PROCESSES OF COMPLEX ORGANIC MOLECULES IN THE VAPOR PHASE.[1]

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I. INTRODUCTION

The absorption of ultraviolet or visible radiation produces a transition from the ground state to a higher electronic level of a molecule. This process is usually accompanied by changes in the molecular vibrational (and rotational) energy and is represented by *AB* in figure 1, in which potential energy curves are drawn for the two lowest electronic states of a diatomic molecule.

The metastable excited molecule may lose its electronic energy by the emission of resonance radiation *BA* or of fluorescence *CD* after a period of 10^{-8}–10^{-9} sec., by collisional deactivation which may lead to chemical change within this period, by undergoing a radiationless transition at some point *G* to a second excited state which then dissociates, or, if the absorbed quantum is of sufficient energy, i.e., greater than *AE*, the excited molecule may dissociate directly into atoms at *J*. Moreover, if the potential energy curves for the ground and excited states cross at any point, the excited molecule may undergo a radiationless transition to the corresponding vibrational level of the ground state.

Emission of fluorescence follows the collisional removal of the excess vibra-

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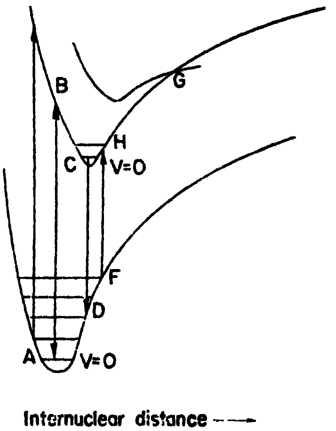

Fig. 1

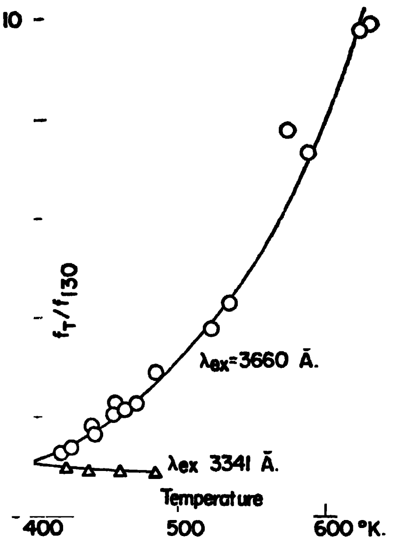

Fig. 2

Fig. 1. Potential energy curves for the ground and fluorescent states of a diatomic molecule.

Fig. 2. The temperature dependence of anti-Stokes fluorescence intensity exhibited by β-naphthylamine at 3660 Å. (56).

tional energy *BC* of the excited molecule within its lifetime and is associated with transitions from its lowest vibrational level *C* (14); thus the fluorescence spectrum is independent of the absorbed frequency within certain limits, and under normal conditions a Stokes emission of lower energy than that of the absorbed quantum is observed. At higher temperatures of the vapor a smaller absorbed quantum may be supplemented by additional vibrational energy *AF* of the ground state (figure 1), in which case the fluorescence is of greater energy than absorbed, *FH*, and is referred to as anti-Stokes.

At very low vapor pressures such that the excited molecule undergoes no collision, its excess vibrational energy is not removed and a resonance emission is observed which is associated with transitions from the initially formed level *B*, and which is therefore dependent on the frequency of absorbed radiation (111).

The term fluorescence "quenching" is here defined as the collisional deactivation of the potentially fluorescent state of the molecule; if this is effected by unexcited molecules of the same species the process is referred to as "self-quenching." In the simplest case in which absorption is followed either by the quenching of fluorescence or by the emission of fluorescence, the ratio of the fluorescence intensity (f_0) emitted by a certain volume of vapor to that (f) emitted by the same volume of vapor in the presence of quenching gas at concentration [Q], other conditions being the same, is given by expression I,

$$\frac{f_0}{f} = \frac{1}{\gamma} = 1 + \frac{k_q}{k_f}[Q] = 1 + K_Q[Q] \qquad \text{(I)}$$

where γ is the quantum yield of fluorescence in the presence of quenching gas, k_q and k_f are the rate constants of the second-order quenching and first-order emission processes, respectively, and K_Q is the quenching constant of gas Q. If z is the quenching collision frequency and p the probability of quenching on collision, expression I becomes

$$f_0/f = 1 + p\tau_0 z \tag{II}$$

where τ_0, the unperturbed lifetime of the fluorescent molecule, is related to the emission probability k_f by

$$\tau_0 = 1/k_f \tag{III}$$

Thus fluorescence-quenching measurements may be used to determine the rates of very fast quenching reactions, provided τ_0 can be determined independently; alternatively τ_0 may be estimated if reasonable assumptions are made concerning z and particularly p. Expression II was first used by Stern and Volmer (87) to obtain the lifetime of the excited iodine molecule from self-quenching data (110).

Excited atoms and simple molecules are very susceptible to collisional deactivation either by foreign gas molecules or by molecules of their own species; thus 0.2 mm. of hydrogen is sufficient to reduce the intensity of resonance emission of mercury vapor by 50 per cent (95), whilst at a pressure of 0.078 mm. the fluorescence intensity per iodine molecule is reduced to one-half its extrapolated value at zero concentration (110). The excited states of certain complex molecules, on the other hand, are found to be particularly resistant to collisional quenching, so that their fluorescence is observed even in solution where the excited molecule suffers some 10^5 collisions with solvent molecules during its lifetime. The chief classes of such fluorescent species are (14): (*a*) The ions and complexes of transition elements in which outer electron shells protect excited inner electrons from collisional perturbation; the fluorescence of this class has not been observed in the vapor phase. (*b*) Organic molecules containing conjugated systems of π-electrons, the excitation of which has little effect on molecular structure and stability. These compounds are fluorescent in both condensed and vapor phases and form the subject of this review. It has been proposed (27) that a condition for the observation of vapor fluorescence at moderate pressures is that two or more canonical structures may be written for the molecule in its ground state; this suggests that the excited electron is delocalized.

The optical behavior of simple molecules has been well established from the analysis of their discrete spectra. In the case of complex organic vapors the fewer characteristics of their continuous spectra exclude the standard methods of structural analysis and necessitate the use of photometric methods (59). It is for this reason, together with the commercial exploitation of the photoelectric effect, the necessity of pure samples, and a knowledge of their vapor pressures, that the quantitative investigation of the luminescence of organic vapors is comparatively recent. It is significant that in a discussion held in 1939 (27) on the "Fluorescence and Photochemical Kinetics of Polyatomic Molecules in the Gas Phase" only nitrogen dioxide and acetone were cited as examples.

The quenching of fluorescence in solution has been reviewed (14, 76), and comparisons of quenching data obtained in the vapor phase and in solution have been made (16, 23) which provide information on the nature of diffusion-controlled processes in the liquid phase (54, 65). In the gas phase the collision rate can be carefully controlled, and this, together with the possibility of dissociation as a process competing with the emission of fluorescence, enables vibrational energy transfer to be investigated from the stabilization of fluorescence. Since this collisional transfer involves one particular aspect of the general photokinetic scheme, this review is written in an attempt to place this aspect in perspective with regard to the scheme as a whole.

II. THE GENERAL PHOTOKINETIC SCHEME

As the complexity of a fluorescent molecule increases, processes other than those of the simple Stern–Volmer scheme become important, so that although the quenching of fluorescence may be expressed by equation 1, the measured quenching constants are not necessarily the ratio of second-order deactivation to first-order emission rate constants. Some theoretical cases have been examined by Henriques and Noyes (27), who point out that a study of the effects of several variables on the intensity of fluorescence will frequently give much information concerning the photokinetic processes taking place; the most probable of these are tabulated and discussed below.

$$\mathrm{F} + h\nu \rightarrow \mathrm{F}^{*\prime} \tag{1}$$

$$\mathrm{F}^{*\prime} \rightarrow \text{dissociation} \tag{2}$$

$$\mathrm{F}^{*\prime} \rightarrow \mathrm{F}' \text{ or } {}^{3}\mathrm{F} \tag{3}$$

$$\mathrm{F}^{*\prime} \rightarrow \mathrm{F} + h\nu \tag{4}$$

$$\mathrm{F}^{*\prime} + \mathrm{X} \rightarrow \mathrm{F}^{*} + \mathrm{X}' \tag{5}$$

$$\mathrm{F}^{*\prime} + \mathrm{F} \rightarrow \mathrm{F}^{*} + \mathrm{F}' \tag{6}$$

$$\mathrm{F}^{*\prime} + \mathrm{Q} \rightarrow \mathrm{F}^{*} + \mathrm{Q}' \tag{7}$$

$$\left.\begin{array}{ll} \mathrm{F}^{*\prime} + \mathrm{Q} \rightarrow & (8) \\ \mathrm{F}^{*\prime} + \mathrm{F} \rightarrow & (9) \end{array}\right\}\text{quenching}$$

$$\mathrm{F}^{*} \rightarrow \mathrm{F} + h\nu' \tag{10}$$

$$\left.\begin{array}{ll} \mathrm{F}^{*} + \mathrm{Q} \rightarrow & (11) \\ \mathrm{F}^{*} + \mathrm{F} \rightarrow & (12) \end{array}\right\}\text{quenching}$$

In this scheme F, Q, and X refer to molecules of the fluorescent species, quenching gas, and inert (nonquenching) gas, respectively; the lowest excited singlet state responsible for fluorescence emission (35) is designated by an asterisk, whilst the prime denotes a molecule with vibrational energy in excess of that corresponding to thermal equilibrium. ${}^{3}\mathrm{F}$ refers to the lowest triplet state of F.

A. EXCITATION: PROCESS 1

Excitation is effected by absorption in the visible or near ultraviolet region of the spectrum resulting in a $\pi \rightarrow \pi^*$ transition. Since the fluorescence emission is, except in anti-Stokes fluorescence, of lower energy than that of the absorbed quantum, it is apparent that the absorption product $F^{*\prime}$ is a higher vibrational level of the potentially fluorescent state F^* (14).

The electronic spectra of complex organic molecules consist of several bands associated with transitions to higher electronic levels (41) which may be written

$$F + h\nu \rightarrow F^{**} \qquad (1a)$$

It is found, however, that regardless of the electronic level excited, the resultant fluorescence emission lies in the same spectral region as that produced by absorption in the first ultraviolet band; this evidence is summarized in Kasha's rule (35) that the emitting level of a given multiplicity is the lowest excited level of that multiplicity. Thus reaction 1a when it occurs must be followed by reaction 1b.

$$F^{**} \rightarrow F^{*\prime} \qquad (1b)$$

Examples of this "cascade" process which may involve several electronic levels, as in tesla-luminescence (2, 3) and scintillation counters (9, 11), are found in β-naphthylamine (56) and in anthracene (52, 77). In the latter case the vapor fluorescence spectrum extending from 3590 Å. to 4300 Å. is excited by absorption in both the 2500 Å. and 3660 Å. regions, with the shorter wavelength producing a broad emission continuum of higher intensity owing to the much larger absorption coefficient at 2500 Å. Luckey, Duncan, and Noyes (49) observed that the short-wave end of the fluorescence spectrum of acetone vapor lies at 26,000 $\mathrm{cm.}^{-1}$, whilst the lowest frequency band in absorption is near 30,800 $\mathrm{cm.}^{-1}$; this indicates that emission and absorption are associated with different excited electronic levels.

The excitation of anti-Stokes fluorescence may be written

$$F' + h\nu'' \rightarrow F^* \qquad (1c)$$

where $h\nu''$ represents a lower energy quantum than that, $h\nu'$, emitted in process 10. The complete fluorescence spectrum of aniline vapor extending from 2800 Å. to 3400 Å. has been observed with small intensity at a vapor temperature of 200°C. with an exciting wavelength of 3900 Å. (73). This large energy deficit in the absorbed quantum is unusual however, and in view of the fact that the absorption spectrum of the vapor does not extend to 3900 Å. even at 200°C., the observation should be repeated before a quantitative explanation is sought. In the case of β-naphthylamine, the vapor fluorescence spectrum extending from 3400 Å. to 4500 Å. is excited by the 3660 Å. line at 130°C. (56). Neporent does not consider this to be a true case of anti-Stokes excitation, yet under these conditions the fluorescence intensity f increases with the vapor temperature T as shown in figure 2. From the linear variation of $\log (f_T/f_{130°})$ with $1/T$ (figure 3) it is concluded that the energy of the absorbed quantum (3660 Å.) is some 1900

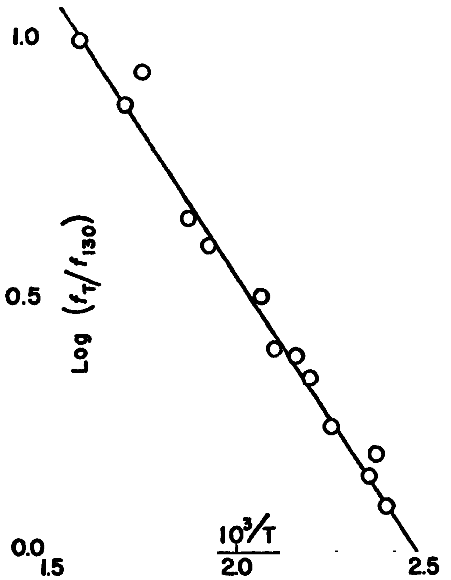

FIG. 3

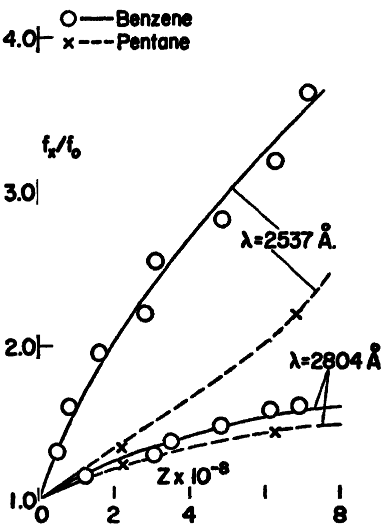

FIG. 4

FIG. 3. Logarithmic-reciprocal plot of data in figure 2

FIG. 4. Fluorescence of β-naphthylamine sensitized by benzene vapor at 2537 Å. compared with typical fluorescence stabilization curve of n-pentane (57).

cm.$^{-1}$ less than the energy difference between the lowest vibrational levels of the ground and excited electronic states of the molecule, which is consequently taken as 29,200 cm.$^{-1}$; this is a useful method for determining the $0'-0''$ band in those cases where both absorption and emission spectra are continuous. At 300°C. part of the fluorescence spectrum of β-naphthylamine in the region 3600–4500 Å. is weakly excited by the 4047 Å. line, and the positive temperature coefficient of the anti-Stokes fluorescence yield has recently been reported for the vapors of 3-amino-, 3,6-diamino-, and 3,6-tetramethyldiaminophthalimide (62).

Electronic excitation may also be effected by energy transfer from a second absorbing species S. This phenomenon of sensitized fluorescence, well known in the solid phase and in solution, may be written:

$$S^* + F \rightarrow S + F^* \qquad (1d)$$

It has been observed for the vapors of acridine, acridonimine, certain phthalimide derivatives, and indigo blue with naphthalene as the sensitizing molecule S in each case (98, 99). Sensitized fluorescence of the relatively nonvolatile complexes aluminum 8-quinolinolate and magnesium phthalocyanine has been observed where direct excitation failed (99), and the large enhancement of the fluorescence of β-naphthylamine excited by the 2537 Å. line on the addition of benzene vapor (shown in figure 4) is attributed to this effect (57). The observation of an anti-Stokes sensitization of the fluorescence of aniline vapor by indigo at 3900 Å. and of the fluorescence of benzene vapor by aniline at 2800 Å. (73, 75) indicates that it is not a necessary condition for sensitization that the sensitizing species should absorb at shorter wavelengths than the emitting molecule.

The tesla-luminescence of benzene vapor has been observed (2, 3), and the excitation of fluorescence by α-particles, x-rays, and γ-radiation is well known in connection with scintillation counters. This review is confined to the processes following the absorption of visible or near ultraviolet radiation.

B. FIRST-ORDER DEACTIVATION OF THE ABSORPTION PRODUCT: PROCESSES 2 TO 4

1. Dissociation

When the energy of the quantum absorbed by a diatomic molecule reaches a critical value, the probability of direct or predissociation increases from zero to a value some several hundred times greater than the probability of emission, fluorescence is no longer observed, the lifetime of the excited molecule decreases sharply, and the absorption spectrum becomes diffuse or continuous (55). Thus in this case dissociation and the emission of fluorescence are mutually exclusive processes.

Of the large number of vibrational modes of a complex molecule, those which are totally symmetric are most strongly excited in an electronic transition; since these would lead to the simultaneous disruption of more than one bond, it is concluded (85) that nontotally symmetric vibrations must be largely responsible for the dissociation of these highly symmetrical molecules. Thus process 2 consists of the stages

$$\mathrm{F}^{*\prime} \rightarrow \mathrm{F}^{*}_{/} \tag{2a}$$

$$\mathrm{F}^{*}_{/} \rightarrow \text{dissociation} \tag{2b}$$

where the subscript denotes an excess of vibrational energy in nontotally symmetric modes. The coupling of totally symmetric with nontotally symmetric vibrations represented by process 2a is brought about by anharmonic forces which increase with the amplitude and energy of the optically excited vibrations. The time required for this internal redistribution of vibrational energy to take place may be of the order of the decay time, in which case fluorescence emission and photodissociation are competing processes over a wide range of absorbed frequencies, with the latter becoming increasingly predominant as this frequency is increased (55, 56).

An increase in the temperature of the vapor excites both symmetric and nonsymmetric vibrations in the ground state. According to the selection rules the excited nonsymmetric vibrations are preserved during the electronic transition so that the production of $\mathrm{F}^{*}_{/}$ according to process 2c

$$\mathrm{F}_{/} + h\nu \rightarrow \mathrm{F}^{*}_{/} \tag{2c}$$

becomes important at higher temperatures (56, 85).

Thus the overall probability of process 2 increases with the total vibrational energy reserve of the molecule which may be excited both optically and thermally

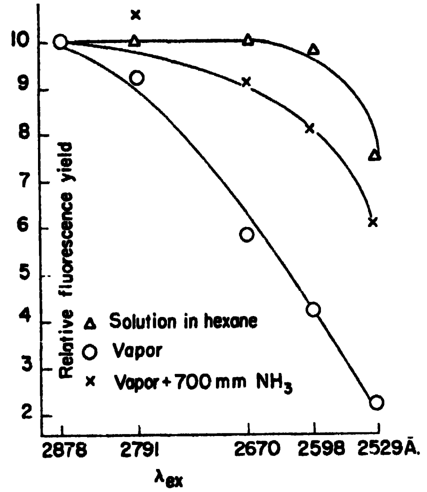

FIG. 5

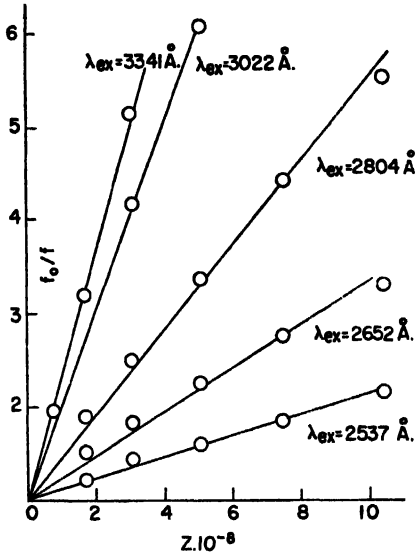

FIG. 6

FIG. 5. Variation of fluorescence yield of aniline with wavelength of absorbed radiation (100).

FIG. 6. Quenching of fluorescence of β-naphthylamine by oxygen at various wavelengths of absorbed radiation (56).

(56, 85). This is manifest in the reduction in the fluorescence efficiency of acetaldehyde (80), acetone (25, 64), aniline (55, 103) (shown in figure 5), β-naphthylamine (56), and certain phthalimide derivatives (61) as the frequency of the absorbed radiation is increased, and the reduced fluorescence efficiency of acetaldehyde (80), aniline (100, 103, 104), β-naphthylamine (56), and the same phthalimides (61) (see table 1) at higher vapor temperatures. Moreover, direct measurements of the quantum yield of dissociation of acetone by the 3130 Å. line show that this approaches unity at temperatures slightly above 100°C. (66).

It is unfortunate that the search for photoproducts obtained during the excitation and measurement of fluorescence has been conducted in so few cases. However, it has been shown (55, 103, 104) that absorption in the region 2800–2500 Å. results in the rupture of the carbon–nitrogen bond in aniline, whilst at shorter wavelengths the aromatic properties of the molecule are destroyed. A similar variation in the mode of disruption with absorbed frequency has been reported in the case of benzene (42, 74), and the production of ethylene in the region 1855–2000 Å. has led Wilson and Noyes (109) to propose the primary process

$$C_6H_6 + h\nu \rightarrow 3C_2H_2$$

for which a symmetric vibration would appear responsible. Following a quantitative treatment of the data for β-naphthylamine it has been suggested (92) that both the mechanism and the rate of the first-order radiationless transition depend on the vibrational energy reserve of the electronically excited molecule; however, there is no direct evidence that either of these deactivation processes involves

TABLE 1

Fluorescence yields (γ) of some phthalimide derivatives in the vapor phase (61)

Molecule	Concentration	λ_{ex}	T	γ
	molecules/cc.	Å.	°C.	
,6-Diaminophthalimide..	$0.1\text{–}2.0 \times 10^{16}$	3850	216	0.014
			265	0.008
			316	0.0045
3-Dimethylamino-6-aminophthalimide...	$0.1\text{–}1.0 \times 10^{16}$	4360	265	0.59
			305	0.52
			355	0.50
3,6-Tetramethyldiaminophthalimide...	1.0×10^{16}	5200	243	0.60
			284	0.46
			335	0.30

dissociation. The relationship of the primary photodissociation process to the emission of fluorescence has been investigated in the case of acetone (48) and biacetyl (82), and has recently been discussed for simple ketones in general (67).

The reduction in the lifetime of the potentially fluorescent molecule owing to process 2 accounts for the observed parallel reduction in the quenching of the fluorescence of aniline by oxygen (55) and the quenching of the fluorescence of β-naphthylamine by oxygen (56) and carbon tetrachloride (22) as the absorbed frequency is increased, according to expression II; the quenching of the fluorescence of β-naphthylamine by oxygen has a negative temperature coefficient for the same reason (56). Figure 6 shows the effect of absorbed frequency on the quenching of the fluorescence of β-naphthylamine by oxygen.

In the case of diatomic molecules, photodissociation can be detected from the diffuse or continuous appearance of their absorption spectra. Owing to the larger number of vibrational modes and closely spaced rotational levels of polyatomic molecules however, their absorption spectra often have a continuous appearance throughout the whole absorption range, and the excitation of fluorescence with high efficiency in some cases (56, 90) indicates that the appearance of an absorption continuum is not an unambiguous criterion for the onset of dissociation (55, 63). Nevertheless the observation of both discrete and continuous regions in absorption has been taken as evidence for dissociation in the latter region in the cases of acetaldehyde (80), acetone (64), aniline (100), naphthalene (108), and benzaldehyde (96).

The conditions for predissociation of polyatomic molecules have been discussed by Sponer and Teller (85), who point out that the phenomenon is more frequently observed than for diatomic molecules, and that the associated diffuse region in absorption may extend over several 100 Å. where dissociation and emission are competing processes. In this case the predissociating state is a different vibrational level of the fluorescent state.

2. Internal conversion

If, in the absence of quenching, the fluorescence yield is found to be less than unity under conditions where process 2 is nonoperative (i.e., in solution (1, 19) or at long wavelengths), this must be due to either process 3a or process 3b or both.

$$F^{*\prime} \rightarrow F' \tag{3a}$$

$$F^{*\prime} \rightarrow {}^3F \tag{3b}$$

Until recent years process 3a was the only recognized alternative, and measurements of the increase in temperature of fluorescent solutions due to this process have been used to obtain fluorescence efficiencies in the dissolved phase (1) which are in good agreement with values obtained directly (17, 19).

However, since the classic work of Lewis and Kasha (44, 45) confirmed previous suggestions (46, 97) associating the well-known phosphorescence of these molecules in rigid media with the lowest triplet state ${}^3F$, the importance of the spin intercombination process 3b has been recognized. Owing to the relatively long lifetime of ca.10^{-4} sec. (72) of the triplet state and its chemical reactivity as a biradical (44), phosphorescence has so far been observed only for the vapors of biacetyl and possibly acetone (38, 45) following ultraviolet absorption, and for acetaldehyde, benzaldehyde, and acetophenone excited by an electrodeless discharge at high pressures (78). However, triplet → triplet absorption spectra have been measured for a number of complex fluorescent vapors, using the flash technique to obtain the necessary high initial concentration of excited molecules (72), and the fact that the probability of the singlet → triplet transition is independent of gas pressure, except possibly at lower pressures, indicates that the process is first order as written.

It has been suggested that one of the two unimolecular deactivations undergone by the excited β-naphthylamine molecule is a spin intercombination process of this type (92); this reduces the fluorescence yield as does dissociation and, apart from the absorption method mentioned above, these processes can only be distinguished by a search for disintegration products, the importance of which is again emphasized.

The evidence indicates that process 3b has a much higher probability than process 3a (35, 37) and is greatly influenced by the presence of heavy or paramagnetic atoms in the molecule (34, 35, 112). Thus, whilst the fluorescence spectra of benzene, fluorobenzene, toluene, benzonitrile, aniline, and benzaldehyde have been obtained (5, 6, 24, 96, 102), substitution of the heavier chlorine atom in the benzene molecule increases the probability of process 3b to such an extent that fluorescence is no longer observed (6).

If the triplet level undergoes a radiationless transition to the singlet ground state (51, 71, 72), as in process 3c, the absorbed quantum appears entirely as

$${}^3F \rightarrow F' \tag{3c}$$

thermal energy (1) and the overall result is that of process 3a.

One further consequence of process 3b is the absence of fluorescence following the weaker $\eta \rightarrow \pi$ transition in nitro compounds, quinones, and simple heterocyclic molecules. The longer-lived $\eta\pi^*$ state undergoes a virtually complete conversion to the triplet level and the phosphorescence yield of these compounds in rigid solvents is close to unity at low temperatures (7, 35).

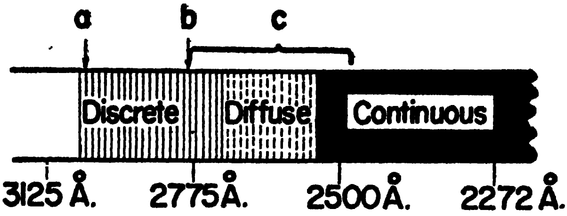

FIG. 7. Schematic representation of absorption spectrum of aniline vapor at low pressures (100).

For further information on the widespread significance of spin intercombinations the reader is referred to the timely and comprehensive review by Kasha and McGlynn (37).[2]

3. *Resonance emission*

Process 4 represents the "resonance" emission observed in the case of benzene (40), aniline (102), and naphthalene (81) at very low pressures. Under these conditions the absorption product $F^{*\prime}$ undergoes no collision and emission occurs before thermal equilibrium of the excited molecule is established. The normal fluorescence is restored, however, if (*a*) the vapor pressure is increased (24, 40, 102), (*b*) inert gases are added (24, 81, 102), (*c*) the temperature is raised (81, 102), or (*d*) the energy of the absorbed quantum is increased (102, 108). Circumstances (*a*) and (*b*) increase the collision rate, and the excess vibrational energy of $F^{*\prime}$ undergoes an intermolecular redistribution as in the case of diatomic molecules; this is not so in cases (*c*) and (*d*). The vibrational energy excited in symmetrical modes reappears in the resonance spectrum as for the diatomic molecule, but if this is sufficiently large it can be internally redistributed amongst nonsymmetric modes according to process 2a before fluorescence emission takes place as discussed above. The excited molecule can then emit if the vibrational energy is insufficient to cause dissociation and the vibrational energy will not contribute to the emitted quantum so that the normal fluorescence spectrum is observed. This emission may be written

$$F^*_{\prime} \rightarrow F_{\prime} + h\nu' \qquad (4a)$$

The intramolecular redistribution of excess vibrational energy of the excited molecule, process 2a, represents a fundamental difference in characteristic between a polyatomic and a diatomic molecule (55). Its probability W depends not only on the reserve of vibrational energy but also on the complexity of the molecule (59); thus the fluorescence spectrum of anthracene vapor remains unchanged (apart from reabsorption effects) even at the lowest pressures (77), indicating that process 2a is completed with the lifetime of the excited state. Neporent (59) has defined a complex fluorescent molecule as one for which $W > 1/\tau_0$, but owing to its energy dependence, W is not a well-defined molecular characteristic; a further subdivision of "complex" molecules has been proposed depending on the magnitude of vibrational and electronic interaction as reflected in the characteristics of both absorption and emission spectra (60). The delicacy of the resonance spectrum can be visualized in the case of aniline, which has the typical absorption spectrum shown in figure 7. At low pressures (0.02 mm.) and room temperature, monochromatic absorption in the region *ab* produces a resonance progression of sharp bands; excitation beyond point *b*, although still in the discrete region of absorption, results in the appearance of normal (continuous) fluorescence. The increase in the absorbed quantum is 5 kcal./mole (100).

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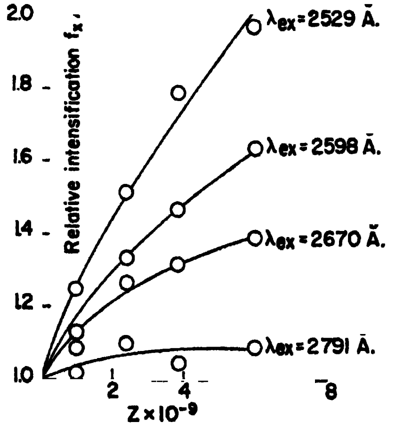
[2] The author is very grateful to Professor Kasha for providing a copy of this review prior to its publication.

C. SECOND-ORDER DEACTIVATION OF THE ABSORPTION PRODUCT: PROCESSES 5 TO 9

1. The establishment of thermal equilibrium

Under conditions such that emission and dissociation are competitive processes it is found that the addition of inert (nonquenching) gases increases the overall fluorescence yield (55, 56, 100). This is attributed to the stabilization of the excited molecule by collisional removal of its excess vibrational energy (process 5), thus reducing the dissociation probability. Figure 5 illustrates the stabilization of the fluorescence of aniline vapor by the addition of ammonia (100), and the relative intensification of the fluorescence of aniline and β-naphthylamine as a function of inert gas pressure is shown at different exciting wavelengths in figures 8 and 9. The effect has also been observed in the case of benzene (55).

A recent interesting observation that inert gases *quench* the anti-Stokes



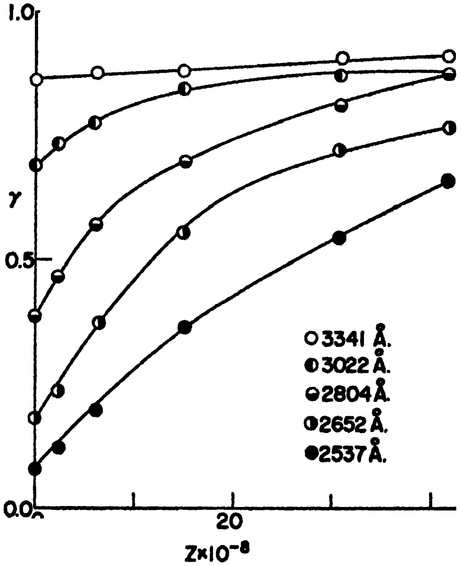


FIG. 8 FIG. 9

FIG. 8. Intensification of fluorescence of aniline vapor by inert gas (ethylene) at different wavelengths (55).

FIG. 9. Effect of inert gas (pentane) on fluorescence yield of β-naphthylamine vapor (57).

fluorescence of 3,6-tetramethyldiaminophthalimide at low pressures is explained in terms of vibrational energy transfer in the reverse direction (12). The lowest vibrational levels of the fluorescent state formed on absorption have less energy than that corresponding to thermal equilibrium which is restored by collision with the inert gas; the increase in the vibrational energy reserve results in a corresponding increase in the rate of dissociation. This process may be written thus:

$$F^* + X' \rightarrow F^{*\prime} + X \qquad (5a)$$

Collisional stabilization increases the lifetime of the fluorescent molecule; this accounts for the increase in measured quenching constant found when ethane and cyclohexane are added to β-naphthylamine quenched by carbon tetrachloride vapor (22). The "flare-up" of luminescence exhibited by the unquenched alpha and poly derivatives of anthraquinone in the presence of nitric oxide is attributed to a similar inhibition of spontaneous dissociation by transfer of the excess vibrational energy of the fluorescent molecule to the foreign gas (33). The very large increase in intensity in this case, however, is probably due to the photochemical production of a second emitting species with a more intense fluorescence in the measured region.

Inert gas molecules in this way remove any dependence of vapor fluorescence on the frequency of the incident radiation, much as solvent molecules in solution do (22). That stabilization by unexcited fluor molecules takes place is evidenced in the change from resonance emission to fluorescence emission of both benzene (24, 40) and aniline (102) as the vapor concentration is increased. This effect, written as process 6, is also produced by inert gases at higher pressures (24, 102), indicating a larger stabilizing efficiency of the "parent" molecule.

There is no apparent reason why quenching molecules should not also behave as inert gases in this respect, and in at least one case process 7 has been accorded a high probability (22). However, it has been observed that oxygen, unlike inert gases, does not cause a redistribution of line intensities in the discrete emission spectrum of aniline at low pressures, but quenches evenly the entire spectrum (102); this suggests that every collision between aniline and oxygen results in quenching.

2. *Electronic deactivation*

The quenching process 8 and 9 must involve the absorption product in view of the immediately preceding remarks. The nature of the quenching process is discussed later.

D. FLUORESCENCE EMISSION: PROCESS 10

By analogy with the behavior of diatomic molecules, emission of fluorescence is associated with transitions from the lowest vibrational level of the first singlet excited state to the various vibrational levels of the ground state (14). This accounts for the fact that the fluorescence spectrum is independent of the magnitude of the absorbed quantum. It is probably more accurate to associate the fluorescence spectrum with transitions from the spontaneous or collision-induced equilibrium population of totally symmetric vibrations in the upper state (91). With the exception of azulene, where a higher excited singlet state is responsible (8, 105), the fluorescent level is in all cases the lowest excited singlet state of the molecule (35), and emission of fluorescence is shown as process 10. In no case has emission of fluorescence been observed from more than one electronic state of the same molecule, although Birks (11) has proposed that the cascade process 1b in anthracene is due to reabsorption of the very fast emission from the higher singlet state produced by absorption at 2500 Å. to form ultimately the lowest excited singlet state which emits the normal fluorescence spectrum. Emission from two excited states of the acetone molecule has been observed (48), but one of these with a lifetime of 10^{-4} sec. has been shown to be the triplet state associated with emission of phosphorescence (38).

If a molecule contains more than one electronic system, as in a substituted aromatic hydrocarbon, each system may absorb independently of the other. Thus the discrete absorption spectrum of aniline in the region 2632–2980 Å. has a band spacing characteristic of the phenyl group (102). In the range 2100–2400 Å. absorption is continuous, with a maximum attributed to the amino group (29); excitation in the latter region produces no vapor fluorescence owing to the high decomposition probability, but absorption in both regions excites the same fluorescence spectrum in solution (55, 100). Some internal transfer of electronic energy must therefore follow excitation of the amino group. In the case of benzaldehyde vapor, Terenin concludes that absorption by the benzene ring excites emission by the carbonyl group (96).

Emission of fluorescence follows the laws of exponential decay and, like the phenomenon of radioactivity, its half-life in the absence of perturbation is insensitive to changes in temperature or pressure and is the same in rigid or fluid media. The emission probability provides the yardstick with which the rates of competing processes may be measured, and it has been suggested (10) that the lifetime τ_0 of the unperturbed molecule has the value of 3.5×10^{-9} sec. for all aromatic hydrocarbons. Until this is confirmed, however, τ_0 must be determined for each molecule before a quantitative interpretation of experimental data is made.

E. SECOND-ORDER DEACTIVATION OF THE FLUORESCENT LEVEL: PROCESSES 11 AND 12

The quenching of fluorescence by foreign gases is found to be specific (22, 55, 56, 90, 102). Oxygen and nitric oxide are the most efficient quenching species, but in those cases where self-quenching has been investigated the unexcited fluorescent molecule is equally potent (90).

The quenching of sensitized fluorescence by oxygen has been observed in mixtures of acridine and naphthalene vapors at 2790 Å.; since pure acridine is unquenched, it must be concluded that oxygen deactivates the sensitizing naphthalene molecule (98).

The mechanism of the quenching process is discussed later.

F. THE OVERALL FLUORESCENCE YIELD

The available evidence suggests that processes 2 to 12 are the most probable ones following the electronic excitation of a complex fluorescent molecule in the vapor phase. The intensity of incident radiation is normally such that even under conditions of complete absorption, the photostationary concentration of excited molecules is negligibly small compared with the total fluor concentration; for this reason second-order processes involving two excited molecules, as well as the effects of dissociation products, may be neglected.

If k_n is the rate constant of process n, then under photostationary conditions when

$$d[F^{*\prime}]/dt = d[F^*]/dt = 0$$

the total intensity f of fluorescence is given by

$$f = k_4[F^{*\prime}] + k_{10}[F^*] \tag{IV}$$

and the overall fluorescence yield γ for the above scheme is related by

$$\frac{f}{I_a} = \left\{\frac{1}{k_2 + k_3 + k_4 + k_5[X] + k_6[F] + k_7[Q] + k_8[Q] + k_9[F]}\right\} \times \left\{k_4 + k_{10}\left(\frac{k_5[X] + k_6[F] + k_7[Q]}{k_{10} + k_{11}[Q] + k_{12}[F]}\right)\right\} \tag{V}$$

where I_a, the intensity of absorbed radiation, is equal to the rate of formation of excited molecules.

Expression V may be simplified by the assumption that the fluorescence decay time is independent of the vibrational level of the fluorescent state, i.e., that $k_4 = k_{10}$. This is perfectly reasonable in view of the fact that processes 4 and 10 concern radiative transitions between the same electronic states. In this case expression V becomes

$$\frac{1}{\gamma} = \left\{1 + \frac{k_{11}[Q]}{k_{10}} + \frac{k_{12}[F]}{k_{10}}\right\} \times \left\{\frac{k_2 + k_3 + k_{10} + k_5[X] + k_6[F] + k_7[Q] + k_8[Q] + k_9[F]}{k_5[X] + k_6[F] + k_7[Q] + k_{10} + k_{11}[Q] + k_{12}[F]}\right\} \tag{VI}$$

It will further be assumed at this stage that the rate of collisional quenching is also independent of the vibrational level of the potentially fluorescent molecule, i.e., $k_8 = k_{11}$ and $k_9 = k_{12}$. This reduces expression VI to

$$\frac{1}{\gamma} = \left\{1 + \frac{k_{11}[Q]}{k_{10}} + \frac{k_{12}[F]}{k_{10}}\right\} \times \left\{1 + \frac{k_2 + k_3}{k_5[X] + k_6[F] + k_7[Q] + k_{10} + k_{11}[Q] + k_{12}[F]}\right\} \tag{VII}$$

Thus the measurement of γ under varying conditions can provide information concerning the rate constants of processes 2 to 12. As the number of constants exceeds the number of variables however, the estimation of a particular rate constant may require the introduction of certain assumptions concerning some of the others, and although the scheme constructed above is useful in predicting the behavior of an excited complex molecule in the vapor phase, each has its peculiar characteristics which must be examined individually.

III. THE DEPENDENCE OF INTENSITY OF FLUORESCENCE ON FACTORS OTHER THAN THE FLUORESCENCE YIELD

The fluorescence yield γ is defined as the ratio of the number of quanta emitted per second to the number of quanta absorbed per second by the same quantity of material. Since the fluorescence radiation is emitted over a relatively wide frequency range in all directions, its total intensity and hence the fluorescence yield is a difficult quantity to determine accurately. In practice a certain frequency range of the emission is measured along one direction, and in order to obtain results of significance, the measuring device should determine a quantity proportional to the number of quanta emitted regardless of frequency (27). Some photoelectric cells and photomultipliers are suitable for this purpose, although their wavelength sensitivity range is relatively restricted and emission spectra must fall within certain frequency limits if they are to be measured in this way.

It is important that any change in the measured quantity should reflect a proportional change in the fluorescence yield, and since the measured intensity in almost all cases differs from the emitted intensity, the possible effects of factors other than the fluorescence yield on both these quantities will be considered briefly.

A. THE EMITTED INTENSITY

By definition the total intensity f of emitted radiation is given by

$$f = I_0[1 - \exp(\epsilon c d)] \times \gamma \tag{VIII}$$

where I_0 is the intensity of the incident beam, and ϵ, c, and d are the absorption coefficient, concentration, and absorption path of the fluorescent vapor, respectively. f will be determined by the following factors.

1. The intensity of incident radiation

For a given volume of gas f is directly proportional to I_0, which must therefore remain constant during a series of related measurements. If the incident intensity is very large however, so that the concentration of excited molecules at any time is appreciable (as in flash photolysis), then second-order processes involving two of these become important and a dependence of γ on I_0 may be expected.

2. The frequency of incident radiation

Since the absorption coefficient ϵ varies considerably with the incident frequency, the latter determines the rate of formation of excited molecules and hence the fluorescence intensity f. It is desirable that the incident radiation be monochromatic, so that the energy of the absorption product is kept within narrow limits and its value can be reliably estimated.

3. The temperature of the vapor

The temperature of the vapor controls the population of vibrational levels in the ground state of the absorbing molecule and any variation will affect the absorption coefficient at a particular wavelength, as in the case of acetone (48) and β-naphthylamine (56). Absorption measurements should therefore be an integral part of any investigation of the temperature coefficient of γ. The temperature coefficient of the vapor concentration c will depend on the method employed for its control.

4. The concentration of fluorescent vapor

The rate of production of excited molecules is determined by the vapor concentration c, which must be taken into account when this is the variable quantity (79, 90). At low concentrations f is directly proportional to c provided ϵ and d are not unduly large; this fact has been exploited in the measurement of sublimation pressures from fluorescence data (89).

5. The concentration of inert gases

The addition of inert gases ensures the establishment of thermal equilibrium of the fluorescent molecule in both its ground and fluorescent states. At very low fluor concentrations the introduction of inert gases may shift the absorption spectrum slightly and change the absorption coefficient at the particular wavelength used for excitation. The effect has been studied quantitatively in the case of β-naphthylamine (58), where the "partial weakening" of fluorescence, owing to a parallel reduction in ϵ, increases with the pressure of helium and other light gases to a maximum at relatively low pressures, as shown in figure 10. It appears that neither the mass nor the radius of the inert gas molecule determines the magnitude of its effect, which decreases in the order He > H_2 > N_2 > NH_3 > CO_2 (58).

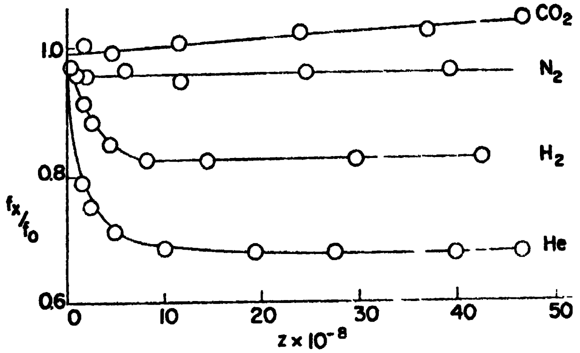


FIG. 10. "Partial weakening" of fluorescence of β-naphthylamine by foreign gases (58). λ_{ex} = 3341 Å.; T = 150°C.; β-naphthylamine pressure = 0.53 mm.

A much larger weakening effect would be expected if the added gas absorbs in the region used for excitation, and the importance of absorption measurements in the interpretation of fluorescence data is emphasized.

6. The concentration of quenching gases

It is necessary to distinguish the quenching process from thermal reactions or photoreactions involving the unexcited fluorescent molecule which effectively reduce the fluor concentration. A suggested interpretation of the quenching of the fluorescence of anthracene vapor by sulfur dioxide in terms of both a thermal reaction of sulfur dioxide with the ground state and a photoreaction with the excited state of the anthracene molecule has been given (90). In this case equation I is not obeyed and the quenching molecule greatly reduces the absorbing power of the fluor.

As with inert gases, the effect of quenching gas on the rate of formation of excited fluorescent molecules should be examined in each case even if the added gas does not itself absorb in the region studied.

B. THE MEASURED QUANTITY

In practice the ratio of the intensity F of part of the fluorescence spectrum viewed in one direction to the intensity BI_0 of a reference beam monitored from the excitation source is measured; in this way errors due to fluctuations in the source are minimized. Differential photomultiplier set-ups have been described for this purpose (16, 21).

Various "optical circuits" have been designed in which the fluorescence is viewed from the front (90) or rear (79) cell surface or at an angle of 90° to the incident beam (16, 21). In each case the filter necessary to remove scattered incident radiation usually absorbs the short-wave region of the emitted spectrum.

The relationship between the measured quantity and the total fluorescence intensity f is clearly

$$F/BI_0 = Af/BI_0 = (A/B)[1 - \exp(\epsilon cd)]\gamma \tag{IX}$$

where A is the fraction of fluorescent radiation intercepted by the measuring instrument. Thus if F_1/BI_0 and F_2/BI_0 are measured under conditions 1 and 2

$$\frac{(F_1/BI_0)}{(F_2/BI_0)} = \frac{f_1}{f_2} = \frac{[1 - \exp(-\epsilon_1 c_1 d)]}{[1 - \exp(-\epsilon_2 c_2 d)]} \frac{\gamma_1}{\gamma_2} \tag{X}$$

and if ϵ and c remain unchanged,

$$\frac{(F_1/BI_0)}{(F_2/BI_0)} = \frac{f_1}{f_2} = \frac{\gamma_1}{\gamma_2} \tag{XI}$$

If F/BI_0 and γ are known under any given set of conditions, then γ can be calculated for any other set of conditions for which F/BI_0 is measured, and expression VII can be used to determine the relative rates of the operative photokinetic processes.

It is essential that both c and ϵ remain unchanged if expression XI is to be valid for measurements made under varying conditions. Any variation in these quan-

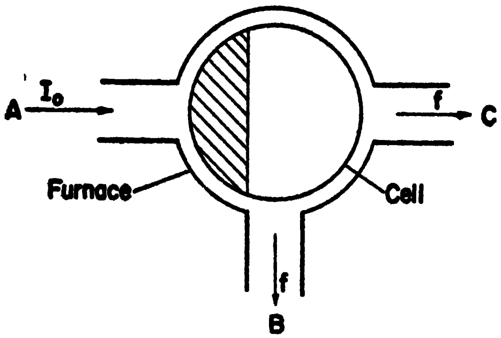


FIG. 11. Plan of typical fluorescence cell illustrating "window effect"

tities should find compensation in the use of expression X, in which respect the following points are made:

(*a*) Since the filters transmit only part of the fluorescence spectrum, the energy distribution of the latter must remain unchanged during a series of related measurements.

(*b*) If the concentration of the fluorescent vapor is the variable quantity, the optical arrangement must be such that measurements are unaffected by changes in the emission "center of gravity." At high vapor concentrations the incident radiation will be almost completely absorbed in the front (shaded area) of the cell shown in figure 11. The emission from this area will not be detected by an instrument placed at B, which will record a maximum intensity at a vapor concentration lower than that required for complete absorption (21, 52, 88). Such an arrangement is particularly unsatisfactory for the measurement of concentration effects and the recording instrument should be placed at either A or C, at a sufficient distance from the cell to minimize effects due to the change in the emission center of gravity in the direction AC (79). One disadvantage of viewing at A and C is that the strong filters necessary to remove the intense reflected or transmitted exciting beam greatly reduce the measurable fluorescence intensity.

(*c*) If an added gas or the fluorescent vapor itself acts as an inner filter by absorbing part or all of the fluorescence spectrum, then changes in the concentration of these molecules will produce results of little significance. The polychromatic nature of the emitted radiation makes a correction for this effect extremely difficult to apply (79), so that foreign gases which absorb in this region should not be used. Usually a fluorescent molecule does not reabsorb the long-wave portion of its emission spectrum which is transmitted by the filters and the errors in this case are not serious (90). If the added gas absorbs the monochromatic incident radiation a correction is easily made, but the kinetic scheme may be further complicated by the presence of electronically excited molecules of a foreign gas.

IV. THE QUANTITATIVE ASPECTS OF FLUORESCENCE QUENCHING

A. THE MEASUREMENT OF QUENCHING CONSTANTS

The ratios of the second-order deactivation to first-order emission rate constants, k_{11}/k_{10} and k_{12}/k_{10}, are referred to as the quenching constants K_Q and

K_F for foreign gas and self-quenching, respectively. Their determination is conveniently illustrated by reference to work on anthracene and β-naphthylamine.

1. Anthracene

Using the 3660 Å. mercury line for excitation at a temperature of 280–340°C., the fluorescence intensity of anthracene vapor has been measured at various pressures and in the presence of inert and quenching gases (90).

It was found that

(*a*) The fluorescence yield, when corrected for collisional perturbation, is approximately unity; hence $k_2 = k_3 = 0$.

(*b*) The inert gases hydrogen, nitrogen, argon, ethylene, and hydrogen sulfide have no effect on either the fluorescence yield or the intensity; this confirms the absence of processes 2 and 3, and eliminates process 5 and, by analogy, processes 6 and 7.

(*c*) The quenching constants obtained for oxygen both in a vacuum and in the presence of 760 mm. of nitrogen are in good agreement, supporting the conclusions drawn in (*a*) and (*b*).

Thus expression VII becomes

$$\frac{f_0}{f} = \frac{\gamma_0}{\gamma} = 1 + K_Q[Q] + K_F[F] \qquad \text{(XII)}$$

where f_0 and γ_0 refer to the fluorescence intensity and yield, respectively, in the absence of quenching processes.

K_F was determined from the variation in fluorescence intensity with the concentration of anthracene vapor; the method of frontal illumination was used, and the expression derived (79) for self-quenching in solution, i.e., a form of expression IX was employed to allow for the increased rate of formation of excited molecules with concentration.

K_{O_2} and K_{NO} were obtained from quenching measurements at low anthracene pressures where self-quenching may be neglected and expression XII reduces to expression I. At higher concentrations of anthracene, where self-quenching is appreciable, the reduction in fluorescence intensity from f_0 to f by the introduction of quenching gas is given by expression XIII,

$$\frac{f_0}{f} = \frac{1 + K_Q[Q] + K_F[F]}{1 + K_F[F]} = 1 + K'_Q[Q] \qquad \text{(XIII)}$$

and since [F] remained constant, Stern–Volmer behavior was observed with oxygen and nitric oxide as quenching gases. The measured constants

$$K'_Q = K_Q/(1 + K_F[F])$$

when corrected for self-quenching according to expression XIII, agreed with K_Q obtained at low anthracene pressures and with previous values (16, 53). The quenching data for anthracene, 9-phenylanthracene, and 9, 10-diphenylanthracene are given in table 3.

2. *β-Naphthylamine*

Curme and Rollefson (22) studied the effect of the inert gases ethane and cyclohexane on the quenching by carbon tetrachloride of β-naphthylamine fluorescence excited by the lines 2537–2650 Å. and 3130 Å. Under these conditions processes 2 or 3 or both are operative (56). These authors neglected the effect of self-quenching, since this would have caused trends in the results which were not observed, and which would in any case be negligible at the low fluor concentrations used; they further assumed that the quenching gas stabilizes, but does not quench, the absorption product, which in this case may be a higher excited singlet state (22, 56). The elimination of process 8 and preference for process 7 is the reverse of the conclusions drawn from the even quenching of the aniline resonance spectrum by oxygen (102), and is unnecessary if the rate constants of processes 8 and 11 are assumed equal, as in expression VII. However, the use of expression V in this case, with k_4 assumed zero, leads to

$$+\frac{k_{11}[Q]}{k_{10}}\Big\}\left\{\frac{k_2+k_3+k_5[X]+k_6[F]+k_7[Q]}{k_5[X]+k_6[F]+k_7[Q]}\right\} \qquad \text{(XIV)}$$

and if f_0 and γ_0 are the fluorescence intensity and yield, respectively, in the absence of quenching gas, then

$$\frac{f_0}{f}=\frac{\gamma_0}{\gamma}=(1+K_Q[Q])\left\{\frac{k_2+k_3+k_5[X]+k_6[F]+k_7[Q]}{k_2+k_3+k_5[X]+k_6[F]}\right\}$$
$$\times\left\{\frac{k_5[X]+k_6[F]}{k_5[X]+k_6[F]+k_7[Q]}\right\} \qquad \text{(XV)}$$

The quantity $(f_0/f-1)/[Q]$ increases with inert gas pressure to a maximum value equal to K_Q as the fractions in XV containing [X] approach unity; the value of 950 liters mole^{-1} is obtained for the quenching constant at both frequencies.

Neporent (56) investigated the quenching by oxygen of the fluorescence of β-naphthylamine at very low fluor concentrations and at various temperatures, using different wavelengths of exciting radiation. Under these conditions second-order processes involving F may be ignored, and in the absence of inert gases stabilization of the absorption product does not take place if, as Neporent justifiably but tacitly assumed, process 7 is negligible. Expression VII is reduced under these conditions to

$$\frac{1}{\gamma}=\left\{1+\frac{k_{11}[Q]}{k_{10}}\right\}\left\{1+\frac{k_2+k_3}{k_{10}+k_{11}[Q]}\right\} \qquad \text{(XVI)}$$

and the quenching is expressed by

$$\frac{f_0}{f}=\frac{\gamma_0}{\gamma}=1+\frac{k_{11}[Q]}{k_2+k_3+k_{10}}=1+K'_Q[Q] \qquad \text{(XVII)}$$

The measured quenching constant K'_Q was found to decrease as either the temperature or the exciting frequency increased, owing to the dependence of processes 2 and 3 on the vibrational energy reserve of the molecule. However, the Stern–

Volmer plots shown in figure 6 are obtained at constant temperature. Neporent translated his quenching data directly into lifetime values as discussed below in Section V,A, but at 3660 Å. and 130°C., under which conditions processes 2 and 3 do not take place, K_Q is calculated to be 3800 liters mole^{-1}. That this is some four times greater than the quenching constant for carbon tetrachloride is attributed to the higher collision frequency and efficiency of the faster paramagnetic oxygen molecule. (See Section IV,B below.)

B. THE MECHANISM OF THE QUENCHING OF FLUORESCENCE

The term "quenching" is usually applied to any process which lowers the fluorescence yield. Thus internal, collisional and inner-filter, compound or "static" quenching have been recognized in solution (14, 16), and thermal quenching in the vapor phase has been used to describe process 2 (100). Here the term will be restricted to the second-order deactivation of the potentially fluorescent molecule; this process appears to be specific and the effect of quenching molecules will be discussed according to their magnetic properties.

1. Paramagnetic quenching molecules

The high efficiency of the paramagnetic molecules oxygen and nitric oxide in quenching the fluorescence of aromatic compounds in the adsorbed (32, 33, 39, 84), dissolved (15, 16, 17, 106, 107), and vapor (16, 26, 31, 55, 56, 90, 102, 103, 104) phases is well known, and the relation of quenching to the photoreaction of the quenched molecule, particularly in solution, has been the subject of several investigations (18, 20, 107).

The reversible nature of the quenching process in the adsorbed and dissolved phases indicates that a photoreaction is not the primary quenching process as suggested for aniline in the vapor phase (104). The simple process

$$F^* + Q \rightarrow F' + Q' \tag{11a}$$

assumes that the electronic energy of F*, which may be of the order of 100 kcal./mole, is transformed into vibrational energy of the colliding partners, and moreover is not specific for paramagnetic molecules.

Kautsky (39) has suggested that quenching by oxygen results in the electronic excitation of the oxygen molecule to one of its low-lying singlet states, $^1\Sigma$ at 37 kcal. or $^1\Delta$ at 22, 27, and 31 kcal. above the ground state (28). This process, which may be written

$$F^* + {}^3O_2 \rightarrow F' + {}^1O_2 \tag{11b}$$

would explain the quenching inability of most inert gases which have no such low-lying electronic levels, but would be expected to have a low probability in the absence of spin conservation which is an important factor in simpler systems (43). Moreover it is found that the nitric oxide molecule, with a lowest excited state $^2\Sigma^+$ at some 126 kcal. above the ground state, is just as efficient a quenching molecule as oxygen (26, 33, 48, 90), and the interpretation of quenching as an energy-transfer process cannot be upheld in this case (33).

The theory of paramagnetic quenching introduced by Terenin (97) recognizes the lower-lying triplet state of the fluorescent molecule. According to this theory the restrictions attending singlet → triplet transitions are removed by collision with the paramagnetic oxygen molecule with the possible results

$$\begin{tikzcd}[row sep=small] & {}^3\mathrm{F}' + {}^3\mathrm{O}_2' & \text{(11c)} \\ {}^1\mathrm{F}^* + {}^3\mathrm{O}_2 \arrow[ur] \arrow[dr] & & \\ & {}^3\mathrm{F}' + {}^1\mathrm{O}_2 & \text{(11d)} \end{tikzcd}$$

Of these, Terenin considered process 11d the most probable, since the requirements of spin conservation are met. Moreover, process 11d reduces the amount of energy which must be taken up vibrationally between the colliding partners and requires that the energy liberated in the singlet → triplet conversion should be sufficient to excite the oxygen molecule to its singlet state, i.e., F^* should lie at least 22 kcal. higher than ^3F. From his suggested association of phosphorescence emission with ^3F, Terenin assigned the range of energy values 35–70 kcal. to the latter and predicted that the fluorescent state must have an energy of at least 57 kcal., corresponding to absorption at 5000 Å., for quenching to take place by process 11d.

Karyakin (31) subsequently investigated twenty-five derivatives of anthraquinone in the vapor phase and found that of eleven which did not react with oxygen in the dark at 300°C., those with an absorption maximum in the range 4500–4800Å. were reversibly quenched by oxygen, whilst those with maxima in the region 5500–5600 Å. were unaffected. However, further quenching studies carried out with the same derivatives in both adsorbed and vapor phases, using the paramagnetic nitric oxide molecule, produced parallel results (33); in view of the large energy required for the electronic excitation of nitric oxide this result eliminates 11d as the quenching process.

Despite the infringement of spin conservation requirements, process 11c appears to be the most tenable at the present time. It has been suggested that the fluorescent and triplet levels should lie within 5 kcal. of each other for quenching to occur (32), but in view of their large separation of 28.7 kcal. in anthracene and 15.5 kcal. in aniline (34), both of which are strongly quenched, this requirement does not appear to be essential. The energy liberated during the singlet → triplet transition can be readily accommodated by the latter state (43) until it is dissipated by further collision, and the formation of photoproducts (20, 107) would then result from secondary processes involving the metastable biradical (18, 97).

The interpretation of quenching by paramagnetic molecules as a collision-induced singlet → triplet transition provides a further example of the influence of strong external magnetic fields on spin intercombinations (35, 37).

2. Diamagnetic molecules

(*a*) *Carbon tetrachloride:* In view of the "heavy-atom" effect on spin-orbital coupling forces (35, 50) it is reasonable to suppose that this molecule quenches the fluorescence of β-naphthylamine (22) by promoting a radiationless singlet → triplet transition on collision. The quenching of the fluorescence of anthracene in solution has received interpretation along these lines (18), and the absence of fluorescence emission by chlorobenzene (6), discussed in relation to the spontaneous transition 3b, suggests that the field near the chlorine nucleus is sufficiently powerful to effect this transition (50). The low efficiency of collisional quenching (see table 3) compared with oxygen may signify that a closer penetration (36) of the colliding molecules is required than that afforded by a kinetic collision.

Carbon tetrachloride has no effect on the fluorescence intensity of anthracene vapor however (90), and its quenching of β-naphthylamine may be the result of a photoreaction involving the amino group. The constant rate of decrease in the fluorescence intensity of this vapor, following the initial sharp reduction when carbon tetrachloride is first added (22), certainly suggests a mechanism of this type. It is unfortunate that the reversibility of the quenching process in the vapor phase is difficult to demonstrate in the majority of cases.

(*b*) *Sulfur dioxide:* Using a static system, Bowen and Metcalf (16) found that sulfur dioxide quenched the fluorescence of anthracene vapor with the same efficiency as oxygen. This may be due to the heavy-atom effect of sulfur described above, although the high efficiency would not be expected. It was later found, however (90), that a marked reduction in the absorbing power of anthracene at 3660 Å. took place on the addition of this quenching molecule; the effect increased both with time and with concentration of the quencher, and the measured quenching constant under flow conditions was found to increase with pressure of sulfur dioxide. These results were interpreted in terms of a reaction of the sulfur dioxide with both ground and excited states of the fluorescent molecule, and a collisional quenching efficiency is obtained which is close to the value for carbon tetrachloride (see table 3). The high value of the quenching constant for sulfur dioxide recently obtained under flow conditions and its independence of flow rate (53) suggest that the above interpretation is insufficient; however, the absence of absorption data in the presence of sulfur dioxide makes it impossible to determine how much of this large quenching effect involves the excited fluorescent molecule.

TABLE 2

Dependence of quenching of fluorescence of anthracene vapor on temperature

Quenching Molecule	Concentration	K_Q		E_Q
		200°C.	300°C.	
	moles/liter	*l./mole*	*l./mole*	*cal.*
SO_2 .	5×10^{-4}	2180 ± 60	2210 ± 14	630
O_2	10^{-3}	932 ± 3	917 ± 4	590
HI..	2×10^{-3}	291 ± 10		
CH_3I	1.2×10^{-2}	77.4 ± 2	59 ± 0	1940
C_2H_5I ..	1.2×10^{-2}	104 ± 3	79 ± 3	1900
$C_5H_{11}I$.	7×10^{-3}	182 ± 10	139 ± 2	1860
Aniline	9×10^{-3}	90 ± 6	47	4000

TABLE 3

Lifetimes from quenching data

Fluor	Quencher	λ	T	K_Q	p	r_F	r_Q	$10^9\tau_0$	References
		Å.	°C.	*l./mole*		Å.	Å.	*sec.*	
Aniline.	O_2	2878	70		1	3.0	1.5	7.9	(55)
β-Naphthylamine.	O_2	3660	130		1	3.5	1.5	16.2	(56)
	CCl_4	2650	120	950	0.4*	3.9	1.7	16.2	(22, 23)
	CCl_4	3130	120	950	0.4*	3.9	1.7	16.2	(22, 23)
Anthracene	Self	3660	300	1280	1	3.3	3.3	4.2	(90)
	O_2	3660	300	1000	1	3.3	1.7	3.2	(90)
	O_2	3660	310	1070	1	3.3	1.7	3.4	(90)
	O_2	3660	220		1	4.1	1.5	2.0	(83)
	NO	3660	280	1120	1	3.3	1.7	3.5	(90)
	HI	3660	200	290	0.4*	3.3	2.0	3.5	(53)
	SO_2	3660	280	340	0.3*	3.3	2.5	3.5	(90)
9-Phenylanthracene	O_2	3660	300	1260	1	4.3	1.7	2.8	(90)
	NO	3660	300	1380	1	4.3	1.7	3.0	(90)
9,10-Diphenylanthracene	Self	3660	300	2200	1	5.1	5.1	4.1	(90)
	O_2	3660	300	1850	1	5.1	1.7	3.3	(90)
Anthraquinone	O_2		300		1			1.3-9.1	(31)
Anthrone	O_2		300		1			5.4	(31)
β-Aminoanthraquinone.	O_2		300		1			5.4	(31)
β-Methylanthraquinone.	O_2		300		1			2.3	(31)

* Calculated assuming τ_0.

(*c*) *Cyanogen:* Neporent (55) observed a reduction in the fluorescence intensity of aniline vapor on the addition of cyanogen. As this author pointed out, cyanogen rapidly polymerizes or reacts with aniline under the influence of ultraviolet radiation, and the deposition of opaque products on the cell walls made quantitative measurements impossible.

(*d*) *Hydrogen iodide and alkyl iodides.* The quenching of the fluorescence of anthracene by these gases (53), shown in table 2, may be attributed to the collisionally induced spin intercombination promoted by the heavy iodine atom, which has been visually demonstrated in the liquid phase (36). The collisional quenching efficiency of hydrogen iodide is some 30 per cent of the value calculated for paramagnetic molecules (table 3) and is close to that for carbon tetrachloride obtained from β-naphthylamine quenching.

The long-wave end of the absorption continua of hydrogen iodide (28), methyl iodide (70), and ethyl iodide (69) is at 3600 Å., close to the wavelength used for excitation (3660 Å.), and the possibility of inner-filter effects at the prevailing temperatures of 2 to 300°C. cannot be ruled out.

(*e*) *Self-quenching:* In this case neither the paramagnetic nor the heavy-atom quenching mechanism can be invoked. Although triplet-level formation has been observed in anthracene vapor in the absence of paramagnetic molecules or heavy atoms (72), it is unlikely that the triplet level is the self-quenching agent, since its photostationary concentration is too small to account for the magnitude of the observed effect (90). Triplet-level formation may be the result of self-quenching in this case according to expression 12a.

$$F^* + F \rightarrow {}^3F + {}^3F \qquad (12a)$$

For anthracene with excited singlet and triplet levels at 27,600 and 14,700 cm.$^{-1}$, respectively, above the ground state (44, 68), process 12a would be energetically feasible, but as a result of their triplet-level absorption studies, Porter and Wright (72) conclude that triplet formation from the fluorescent state is essentially the first-order process 3b followed by collisional stabilization.

In those cases where self-quenching has been quantitatively studied, it is found to be as efficient as paramagnetic quenching (90), and the fluorescence of acetone, as distinct from its phosphorescence (38), is subject to self-quenching whilst oxygen has no effect (48).

(*f*) *Aniline:* A small quenching effect has been observed in anthracene vapor on the introduction of aniline (53, 83). In view of the weak excitation of aniline anti-Stokes fluorescence (73) under conditions similar to those employed, however, the interpretation of this quenching as an inner-filter effect should be considered.

C. THE INTERPRETATION OF QUENCHING DATA

If r_F and r_Q are the radii of fluorescent and quenching molecules and M_F and M_Q are their molecular weights, respectively, then the ratio of collisional deactivation to emission rate constants given by expression II becomes

$$K_Q = \frac{k_q}{k_f} = p\tau_0 \frac{N}{1000} (r_F + r_Q)^2 \left\{8\pi RT \left(\frac{1}{M_Q} + \frac{1}{M_F}\right)\right\}^{1/2} \exp\left(-E_Q/RT\right) \qquad (XIX)$$

where N is Avogadro's number, R is the gas constant, T is the temperature of the vapor, and E_Q is the activation energy of the quenching process.

The analysis of quenching data involves the assignment of values to two of the quantities p, τ_0, and r and evaluation of the third on the assumption that E_Q is zero.

1. *The activation energy of the quenching process*

The estimation of E_Q from quenching measurements requires the determination of the temperature coefficients of all other photokinetic processes which are operative under the conditions of observation. Neporent (56) established that the quenching of β-naphthylamine fluorescence by oxygen is temperature-independent over the range 130–193°C. when the incident wavelength is such (3660 Å.) that no first-order dark deactivation takes place. The quenching by oxygen of the long-lived fluorescence of acetone is also temperature-independent between 32°C. and 75°C. (67), and the increased quenching of the fluorescence of anthracene by oxygen with temperature is only slightly greater than would be expected from the increased collision rate (16).

More recently Metcalf (53) has investigated the quenching effect of several gases on the fluorescence of anthracene excited by the 3660 Å. line at 200°C.

and 300°C. His results, given in table 2, show a negative temperature coefficient and are expressed as

$$K_Q = AT^{1/2} \exp (+E_Q/RT)$$

where A is the temperature-independent factor in expression XIX. Metcalf compared E_Q with E', calculated from the temperature dependence of viscosity η, using the expression

$$\eta = \eta_0 T^{1/2} \exp (+E'/RT)$$

and concluded that the negative temperature coefficients of quenching are no greater than can be attributed to the attractive forces between the fluorescent and quenching molecules. The experimental values of E_Q are small however, and in the case of oxygen and sulfur dioxide the measured quenching constants at the two temperatures are almost identical within the remarkably small experimental error.

Some theoretical evidence may be adduced in support of the assumption that E_Q is zero. There is little doubt that transitions from higher vibrational levels of the fluorescent state take place during fluorescence emission (13, 57, 86), which is therefore represented by both processes 4 and 10. The complex expression VI reduces to VII only if the rate constants of processes 8 and 11, and 9 and 12, are the same; in the absence of processes 2 and 3 expression VII is that proposed by Stern and Volmer, which satisfactorily expresses the quenching data in almost all cases.

2. The lifetime of the fluorescent state

In the absence of internal or collisional perturbations the lifetime τ_0 of the excited molecule is equal to the reciprocal of the emission rate constant, i.e.,

$$\tau_0 = 1/k_{s0}$$

The estimation of τ_0 from quenching data involves assumptions concerning the probability p of quenching on collision and the application of a correction for processes 2 and 3 where these occur. The following arguments have been presented for the assumption that, at least in the case of paramagnetic quenching, p is unity.

(*a*) If quenching by oxygen and nitric oxide is to be interpreted as a collision-induced radiationless singlet → triplet transition under the influence of their magnetic fields, it would be expected that oxygen with an effective Bohr magneton number μ_{eff} of 2.83 would be more efficient than nitric oxide, for which μ_{eff} is 1.92 at 300°C. (101). That both gases are equally efficient in quenching the fluorescence of acetone (48), anthracene (90), anthraquinone derivatives (33), and β-naphthylamine (26) is a strong indication that quenching takes place at every collision (90).

(*b*) At low aniline pressures, the introduction of inert gases strongly increases the intensity of some lines in the resonance spectrum, in particular the line at 2957.6 Å. These gases have no effect on the absorption spectrum; therefore intensification must be due to a collisional redistribution of vibrational energy of the excited molecule. Oxygen strongly quenches the resonance emission but has no effect on the relative intensities of the resonance lines; it is therefore concluded that every collision between an excited aniline molecule and oxygen leads to quenching (55, 102). This argument also supports the assumption that process 7 does not take place.

(*c*) Neporent (56) states that the satisfactory agreement between values for the fluorescence yield of β-naphthylamine measured directly and the values calculated from quenching by oxygen on the assumption that p is unity, indicates that this assumption is correct. However, since γ is calculated as the ratio τ/τ_0, where τ is the lifetime in the presence of first-order deactivation processes 2 and 3, this agreement would still hold if p were not unity but had the same value in each determination, i.e., $\gamma = p\tau/p\tau_0$; as it has been shown that p is independent of the wavelength used for excitation (55), the validity of this argument is doubtful.

Values of τ_0 calculated from quenching data on the assumption that $p = 1$ and using radius values determined from transport phenomena or calculated from molecular models are given in table 3.

By definition the lifetime of the excited molecule is equal to the reciprocal of the sum of probabilities of first-order or second-order deactivating processes. Thus processes 2 and 3 reduce the unperturbed lifetime τ_0 to τ, where

$$\tau = 1/(k_2 + k_3 + k_{10}) \qquad \text{(XX)}$$

and equation XVII becomes

$$f_0/f = 1 + p\tau z \qquad \text{(XXI)}$$

On the justifiable (102) assumption that $p = 1$, Neporent used equation XXI to obtain the values of τ given in table 4 from his quenching data (56).

3. The collisional efficiency of the quenching process

If a reliable value for the lifetime of the excited molecule is available independently, quenching data may be used to determine the collisional quenching probability p. Several authors have preferred to express their results in this way.

Since the probability of emission is equal to the probability of the reverse transition, τ_0 is related to the area under the corresponding absorption band $\int \epsilon' d\bar{\nu}$ with a maximum at $\bar{\nu}_A$ by expression XXII (45)

$$1/\tau_0 = 8\pi c n^2 \bar{\nu}_A^2 \int \epsilon' d\bar{\nu} \qquad \text{(XXII)}$$

where ϵ' is the extinction coefficient in natural units, c is the velocity of light in a vacuum, and n is the refractive index of the medium. Bowen and Metcalf (16) used expression XXII to obtain $\tau_0 = 1.33 \times 10^{-8}$ sec. for the excited anthracene molecule from its absorption band in the near ultraviolet, and concluded from their data that oxygen and sulfur dioxide quench the excited anthracene molecule once in every two to six collisions.

TABLE 4

Lifetimes ($\tau \times 10^{-8}$ *sec.*) *of excited β-naphthylamine molecule from oxygen quenching* (56)*

T	λ = 3660 Å.	3341 Å.	3129 Å.	3022 Å.	2804 Å.	2652 Å.	2537 Å.
°C.							
130	1.62	1.51	1 30	1.19	0.815	0.385	0.195
151	1.62	1.41	1.24	1.12	0.685	0.355	0.165
172	1.62	1.33	1.12	1.04	0.600	0.205	0.140
193	1.62	1.28	1.08	1.00	0.495	0.230	0.105

* Calculated from equation XXI, using r = 3.5 Å. and r_Q = 1.49 Å.

The phase-shift technique has recently been employed to measure decay constants directly in both the dissolved and the crystalline states (4, 47); the high accuracy of this method is somewhat offset by reabsorption effects (4). Bowen has discussed the values obtained for anthracene in this way with those obtained less directly in solution, and uses the most consistent value to interpret vapor-phase quenching data on the reasonable assumption that τ_0 is the same in all phases; he concludes that for oxygen and nitric oxide p is approximately 0.3 (15).

Analysis of the quenching of the phosphorescence of biacetyl by oxygen leads to 0.0095 for p (38). This remarkably low value for the collisional quenching probability between two biradical states suggests that a primary photoöxidation with stringent steric requirements is responsible.

4. *The quenching radius*

Stevens (88) has defined a quenching collision and uses values obtained for the lifetime in solution from expression XXII to obtain a self-consistent set of quenching radii. These are some 60 per cent of the gas kinetic values and are compared with the dimensions of the π-electron systems and paramagnetic fields of the fluorescent and quencher molecules, respectively.

V. QUANTITATIVE ASPECTS OF FLUORESCENCE STABILIZATION

A. FIRST-ORDER DEACTIVATION OF THE POTENTIALLY FLUORESCENT MOLECULE

If the fluorescence yield is unity at very low pressures in the absence of quenching gas, processes 2 and 3 may be assumed nonoperative as in the case of anthracene excited by the 3660 Å. line at 300°C. A lower yield in the absence of second-order perturbations may be due to either process 2 or process 3 or both as suggested for 9,10-diphenylanthracene (90); in this molecule the energy of the carbon–carbon bonds is close to the energy of the absorbed quantum (78 kcal. at 3660 Å.), whilst in support of process 3 the suggested temperature-dependent internal dissociation to the biradical or triplet level (30) may be cited.

In the absence of data on fluorescence yield, the stabilization or enhancement of fluorescence by the introduction of inert gases may be taken as a definite indication that process 2 or 3 is taking place; an analysis of photoproducts, which would be different in each case, will establish whether the deactivation is due to dissociation or to a singlet → triplet transition. The rate of both processes increases with the vibrational energy reserve of the excited molecule, and the resulting

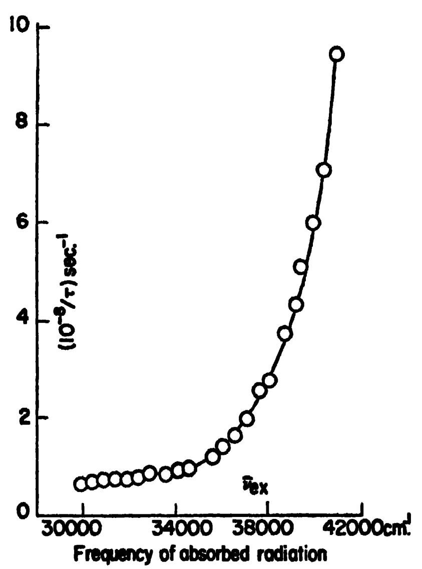


FIG. 12

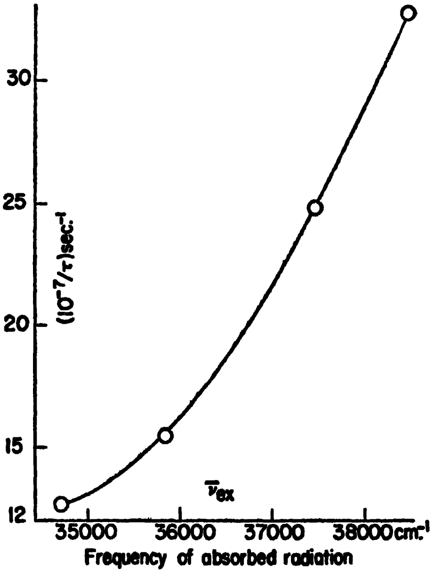


FIG. 13

FIG. 12. Dependence of lifetime τ of excited β-naphthylamine molecule on frequency $\bar{\nu}_{ex}$ of absorbed radiation (56).

FIG. 13. Variation of lifetime τ of excited aniline molecule with frequency $\bar{\nu}_{ex}$ of absorbed radiation (56).

variations of both lifetime and fluorescence yield with the magnitude of the absorbed quantum are shown in figures 5, 12, and 13.

The lifetime of the β-naphthylamine molecule calculated from quenching by oxygen under various conditions is given in table 4. At 3660 Å. processes 2 and 3 do not take place and $\tau = \tau_0 = 1/k_{10}$; whence $k_2 + k_3$ may be calculated for the rest of the data in table 4 from expression XX.

The probability $d = k_2 + k_3$ of dark deactivation is found to increase exponentially with the reserve of vibrational energy E of the excited molecule, and Neporent (56) proposed the empirical relationship

$$d = A \exp[\alpha(\bar{\nu}_e + q)] \qquad \text{(XXIII)}$$

involving constants A and α, the frequency $\bar{\nu}_e$ of the absorbed radiation, and the measure q of the thermal contribution to E, equivalent to 24 cm.$^{-1}$/°C. in this case. The appropriate plot is shown in figure 14, and the divergence of the low-energy data is attributed (56) to the nonequivalence of the optical and thermal excitation of vibrational energy when this is small; the simultaneous operation of processes 2 and 3 could conceivably produce the same effect.

Boudart and Dubois (13) have assigned a vibrational temperature T_{vib} to the molecule excited by the frequency $\bar{\nu}_e$ at temperature T, defined by

$$T_{\text{vib}} = T + (\bar{\nu}_e - \bar{\nu}_0)/C_{\text{vib}} \qquad \text{(XXIV)}$$

where $\bar{\nu}_0$ is the O′–O″ transition frequency and C_{vib} is the vibrational heat capacity of 24 cm.$^{-1}$/°C. From a suitable plot of the higher-energy data, the first-order rate expression is found to be

$$d = 0.254 \times 10^{13} \exp[-(14{,}300/RT_{\text{vib}})] \qquad \text{(XXV)}$$

but the deviation of the lower-energy data is again apparent (92) and is attributed by these authors to the incomplete internal redistribution of the small amount of vibrational energy during the lifetime of the excited molecule. If this redistribution is incomplete it is difficult to understand why the fluorescence spectrum remains unchanged as E increases (56).

It is apparent that the spectral region investigated by Neporent covers two electronic band systems, and a treatment of the low-energy data obtained, following absorption in the first of these, leads to a value of 40 cm.$^{-1}$/°C. for C_{vib} (92). The use of this value to obtain T^*_{vib} from expression XXIV leads to the expression

$$d' = 0.75 \times 10^{10} \exp[-(5600/RT^*_{\text{vib}})] \qquad \text{(XXVa)}$$

for the low-energy data, which, it is suggested, refer to the radiationless spin-intercombination process 3b. Since T^*_{vib} ranges from approximately 400 to 600°C., d' has the values 10^7–10^8 sec.$^{-1}$, which are well within the limits 10^6–10^9 sec.$^{-1}$ suggested for this process (72).

Although the nature of these processes is uncertain in the case of β-naphthylamine, it has been established (55) that the first-order process competing with the

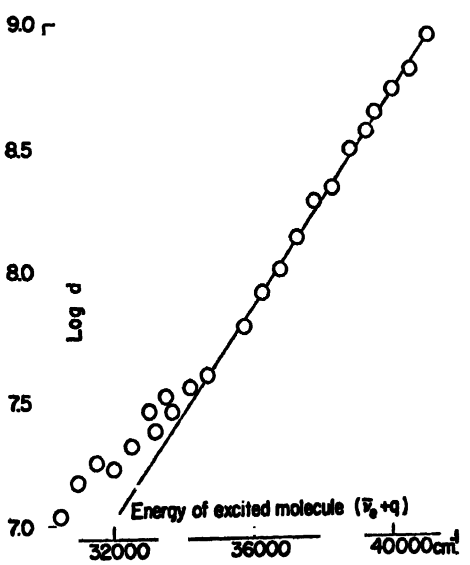


FIG. 14

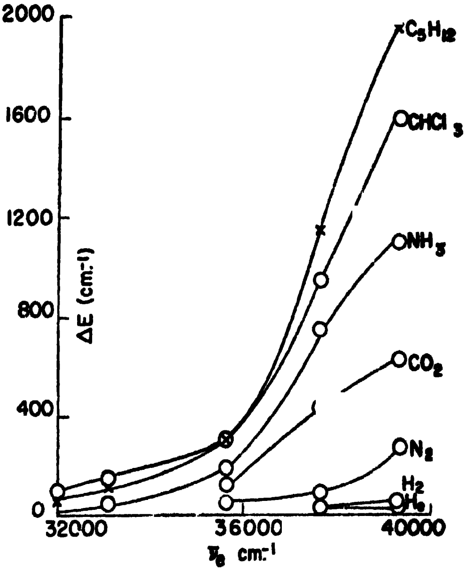


FIG. 15

FIG. 14. Variation of probability d of radiationless deactivation with energy of excited β-naphthylamine molecule according to expression XXIII (56).

FIG. 15. Variation of energy transferred per collision with total energy of β-naphthylamine molecule (57).

fluorescence emission of aniline involves rupture of the carbon–nitrogen bond. A similar treatment of the data for this molecule provides the expression (93)

$$d = 3.6 \times 10^{13} \exp[-(12{,}000/RT_{\text{vib}})] \qquad \text{(XXVb)}$$

and the similarity between this and expression XXV is certainly circumstantial evidence for the dissociation of β-naphthylamine at higher vibrational temperatures.

B. THE COLLISIONAL TRANSFER OF VIBRATIONAL ENERGY

The collisional stabilization of an energy-rich fluorescent molecule (processes 5, 6, and 7) leads to an increase in the overall fluorescence yield according to expression VII. Measurement of this increase as the pressure of stabilizing gas is increased enables the average amount of energy transferred per collision to be determined. This has been done in two ways.

1. *Variation of the measured quenching constant with inert gas pressure*

The quenching of β-naphthylamine fluorescence by carbon tetrachloride in the presence of the inert gases ethane and cyclohexane (22) has been discussed above (Section IV,A). The variation of the measured quenching constant with inert gas pressure is given by expression XV and shown in figures 3 and 4 of reference 22. Curme and Rollefson calculated k_7 from quenching data in the absence of inert gas, assumed that process 6 takes place at every collision, and, with Neporent's value for k_2 under the prevailing conditions, found the value of k_5 which, used in expression XV, gives the experimental curves at each exciting wavelength.

If the vibrational energy of the excited molecule is $(\bar{\nu}_e - \bar{\nu}_0)$ and its collision frequency with the inert gas is k_z, then the average amount of energy ΔE removed per stabilizing collision is given by

$$\Delta E = k_5(\bar{\nu}_e - \bar{\nu}_0)/k_z$$

The results obtained, shown in table 5, are of little quantitative significance in view of the fact that process 6 is assumed to take place at every collision; the interval between collisions under the prevailing conditions is approximately 10^{-7} sec., and this is so much greater than the reduced lifetime (10^{-8}–10^{-9} sec.) of the excited molecule that it is unlikely that process 6 occurs at all.

TABLE 5

Average amount (ΔE) *of vibrational energy transferred from β-naphthylamine molecule per collision* (*22*)

$\lambda = 3130$ Å.; $T = 120$°C.

Stabilizing Molecule	β-Naphthylamine	Carbon Tetrachloride	Cyclohexane	Ethane
ΔE cm.$^{-1}$.	4000	250	250	100

2. *Variation of fluorescence yield with inert gas pressure*

This more elegant and direct method was first employed in the case of aniline (55, 100). At very low pressures in the absence of quenching gas expression VII becomes

$$\frac{1}{\gamma_x} = 1 + \frac{k_2 + k_3}{k_5[X] + k_1} \qquad \text{(XXVI)}$$

Thus if f_0 and f_x are the respective fluorescence intensities in the absence of inert gas and in its presence at concentration [X], the relative intensification of fluorescence Δf is given by

$$\frac{1}{\Delta f} = \frac{f_0}{f_x - f_0} = \frac{\gamma_0}{\gamma_x - \gamma_0} = \frac{k_{10}}{k_2 + k_3} + \frac{k_{10}(k_2 + k_3 + k_{10})}{k_5[X]\,(k_2 + k_3)} \qquad \text{(XXVII)}$$

The plot of $1/\Delta f$ against $1/[X]$ is linear and the slope/intercept ratio gives $(k_2 + k_3 + k_{10})/k_5 = 1/\tau k_5$. Since τ is known from quenching data on oxygen, k_5 may be calculated; the stabilizing efficiencies k_5/k_z obtained in this way are given in table 6.

This treatment has been refined more recently in its application to β-naphthylamine (13, 57). In the first place a correction is applied for the effect of inert gases on the absorption coefficient discussed in Section III,A above by using the ratio S of the stabilization $(f_x/f_0)_\lambda$, measured at the wavelength λ, to $(f_x/f_0)_{3660}$ measured at 3660 Å., where processes 2 and 3 do not take place and the change in fluorescence intensity is entirely due to the "partial weakening" effect (57, 58).

Secondly, it is recognized that the total vibrational energy E of the excited molecule is not removed by one particularly fortunate collision, but that successive collisions each remove a fraction of this energy to produce a descending series of vibrational levels with different probabilities of deactivation.

Neporent (57) treated this problem in a remarkably simple manner by noting the increase in fluorescence intensity produced at the frequency $\bar{\nu}$ when the pressure of added inert gas is such that each excited fluor molecule undergoes on the average one collision. The energy ΔE transferred by this collision is then equal to the reduction in frequency $\Delta\bar{\nu}$ required to produce the same intensification in the absence of inert gas. The results obtained are given in table 7.

Boudart and Dubois (13) have treated the multistage deactivation process

TABLE 6

Stabilization efficiency of inert gas molecules from enhancement of fluorescence of aniline vapor (55, 100)

λ	Ammonia	Ethylene	Nitrogen	Carbon Monoxide	Hydrogen
Å.					
2670	0.09	0.04	—	0.05	0.04
2598	0.09	0.05	0.06	0.07	0.08
2529	0.15	0.10	0.15	0 14	0.20

TABLE 7

Energy-transfer data from stabilization of fluorescence of β-naphthylamine

Gas	λ_{ex}	T	E	ΔE*	ΔE†	α
	Å.	°C.	cm.$^{-1}$	cm.$^{-1}$	cm.$^{-1}$	
CO_2	2652	150	8460	550	430	0.5
	2537	150	10200	600	630	0.3
NH_3	2652	150	8460	950	750	0.9
	2537	150	10200	1070	1100	0.8
	2652	190	8460	880	630	0.8
	2537	190	10200	1000	1250	0.7
C_6H_{12}.	2652	150	8460	1280	1150	0.2
	2537	150	10200	1690	1950	0.2
	2652	190	8460	1240	1350	0.2
$CHCl_3$..	2652	150	8460	1000	950	0.5
	2537	150	10200	1240	1600	0.5
H_2. .	2652	150	8460	70	30	0.1
	2537	150	10200	70	50	0.1
He .	2652	150	8460	70	30	0.2
N_2. .	2652	150	8460	190	90	0.3
D_2‡. . .	2652	186	8460	50	—	
SF_6‡ .	2652	186	8460	570	—	

* Neporent (57).

† Boudart and Dubois' treatment of Neporent's data (13).

‡ Boudart and Dubois' experimental data.

mathematically and show that if, as a result of its first collision, the lifetime of the excited molecule is increased from τ_1 to τ_2, then

$$\left(\frac{dS}{dZ}\right)_{x=0} = \tau_2 - \tau_1 \qquad \text{(XXVIII)}$$

where Z is the collision frequency at inert gas concentration [X], and $(dS/dZ)_{x=0}$ is the slope of the tangent to the stabilization curve (shown in figure 8) at zero [X]. As a result of this collision, an amount ΔE of vibrational energy is transferred, and the temperature of the inert gas molecule rises from T_1 to T_2 whilst that of the β-naphthylamine molecule falls from $T_{1\text{vib}}$ to $T_{2\text{vib}}$; thus if C is the heat capacity of X at constant volume

$$\Delta E = C_{\text{vib}}(T_{1\text{vib}} - T_{2\text{vib}}) = C(T_2 - T_1) \qquad \text{(XXIX)}$$

$T_{1\text{vib}}$ (and hence τ_1) is known from expression XXIV, and τ_2 (and hence $T_{2\text{vib}}$) is calculated from expression XXVIII; thus ΔE can be derived from expression XXIX. The results given in table 7 are also expressed in terms of an accommodation coefficient α, which is a measure of the approximation to equilibrium distribution of vibrational energy between the colliding partners and is defined by

$$= \frac{T_2 - T_1}{T_{2\text{vib}} - T_1} = \frac{C_{\text{vib}}}{C}\left(\frac{\Delta E}{E - \Delta E}\right)$$

This classical treatment of the vibrational energy of a complex molecule depends on the excitation of a large number of natural vibrations of different energies during intramolecular redistribution of initially excited mode, which together with the closely spaced rotational levels makes the collisional transfer of

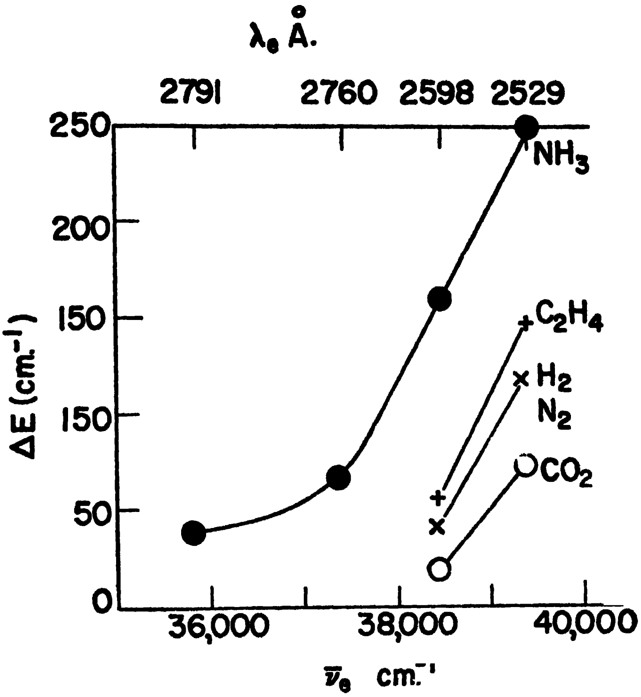


Fig. 16. Variation of energy transferred per collision with total energy of aniline molecule (57).

almost any quantity of energy possible and virtually removes the quantum restrictions (57). This is contrary to the behavior of simple molecules, where the transfer of quanta of larger energy is subject to strict requirements concerning the vibrational levels of the colliding molecules; the characteristics of the transfer process in these two extreme cases have recently been discussed (94).

It is interesting to note that although *n*-pentane removes some twenty times the energy taken up by the helium atom per collision, the efficiencies of these stabilizing gases expressed by α are the same. There is probably some correlation between the high accommodation coefficient of ammonia and the presence of an amino group in the fluorescent molecule, especially since rupture of the carbon-nitrogen bond would require a concentration of energy at this point; in support of this specificity, the pronounced effect of ethylene in stabilizing the benzene molecule (55) may be cited.

The increase in ΔE with the total vibrational energy reserve E is demonstrated for β-naphthylamine in figure 15 and for aniline in figure 16, which is obtained from earlier results (55) following the treatment outlined above (57). The point of inflexion corresponds to the value of E necessary for the internal redistribution of vibrational energy to be complete within the interval (57); it has also been attributed to the onset of a second unimolecular deactivation of higher activation energy which is therefore more susceptible to collisional suppression (92).

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A number of the other Russian papers are available as Technical Translations of the National Research Council of Canada. The author would like to thank the Translations Section of the N. R. C. Library in Ottawa for its cooperation in translating these papers.

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Note added in proof

Bowen and Veljković [Proc. Roy. Soc. (London) **A236**, 1 (1956)] have recently measured the stabilization of the fluorescence of perylene vapor by nitrogen, *p*-cymeme, naphthalene, and hexamethylbenzene and find that, with the exception of naphthalene, the stabilization efficiency is proportional to the molecular weight of the stabilizing molecule. The high efficiency of naphthalene is attributed to a longer collisional duration due to the interaction of π-bond orbitals which promotes thermal equilibration during the collisional process; this view is compatible with the observation that the average amount of energy transferred from the excited β-naphthylamine molecule on collision decreases as the temperature increases (table 7) despite the fact that more thermal energy is available at higher temperatures.

The absence of decomposition products indicates that in the case of perylene the collisionally suppressed deactivation process is the singlet → triplet conversion (process 3b), for which a finite energy of activation must be necessary.

THE PREPARATION AND PROPERTIES OF PHOSPHONIC ACIDS

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I. INTRODUCTION

Among the organic derivatives of phosphorus the phosphonic acids occupy a prominent position. Together with their amides and esters they probably outnumber all other compounds containing the carbon-phosphorus bond. Prior to 1950 no important new methods for preparing this class of compounds had appeared in several decades. In two excellent reviews (127, 128) which cover the chemical literature on organic phosphorus compounds through 1949, the principal methods given for preparing phosphonic acids were the Friedel–Crafts and the Michaelis–Arbuzov reactions, first described in 1879 and 1898, respectively.

After the appearance of these two reviews, however, vastly improved methods for the synthesis of phosphonic acids appeared. With the use of these new methods the number of phosphonic acids prepared has increased tremendously. Since 1950 approximately as many aromatic phosphonic acids have been prepared as were prepared during the previous seventy years.

It is the purpose of this review to cover those methods of preparing phosphonic acids which have appeared since publication of Kosolapoff's two reviews. A list of phosphonic acids prepared since 1950, together with new data on the physical and biological properties of this class of compounds, is included. The phosphonic acids listed are those for which analyses were given or those which were isolated as a syrup and identified by the analysis of a solid derivative. *Chemical Abstracts* is covered through September 25, 1956. Acids mentioned in the literature as having been prepared by the hydrolysis of esters but without further characterization are not listed. The patent literature has been searched, but only those phosphonic acids which have been described in detail are included.

NOMENCLATURE

The nomenclature of organic phosphorus compounds underwent a radical change in 1952. Prior to that year the naming of a new organic phosphorus compound was left largely to the preference of the individual author. *Chemical Abstracts* used a fairly well defined system based on I.U.C. Rule 34, but many authors, writing in American chemical journals, did not follow these rules. In British chemical journals an entirely different system was used, so that the same name was frequently used for describing two different compounds in the two countries. In reading older books on organic phosphorus compounds it is often impossible to ascertain the structure of a compound when only the name is given.

In 1949 an Advisory Committee on the Nomenclature of Organic Phosphorus Compounds was organized within the framework of the Nomenclature Committee of the Division of Organic Chemistry of the American Chemical Society. Several joint sessions were held with a committee of the (British) Chemical Society and a number of compromises were made in an effort to satisfy chemists in both countries. A report was submitted at the meeting of the American Chemical Society in New York in September, 1951. This report was divided into two sections, one dealing with compounds containing one phosphorus atom and the other with compounds containing two or more phosphorus atoms. Tentative acceptance of the first section only was recommended, since full agreement on the second section had not been reached. The report was published almost simultaneously in both *Chemical and Engineering News* (3) and the *Journal of the Chemical Society* (4). The Chemical Society now requires that this nomenclature be used in the *Journal of the Chemical Society*. Although no such definite policy has been officially stated in the various journals published by the American

Chemical Society, the editors of the journals are requesting that this new nomenclature be used. *Chemical Abstracts* also uses this new nomenclature with one or two exceptions. The new system has not been adopted by the International Union of Chemistry nor have chemical journals in countries other than Britain and the United States adopted it. There has been some criticism of the system. It is the opinion of the present authors that the system must be used for some time in order to determine how satisfactory it will be. Undoubtedly, the system is often cumbersome and unwieldy and names many hypothetical classes of compounds which probably never will be prepared. Nevertheless, it does bring order to a very confused state and may well be adopted, at least in part, by the International Union of Chemistry.

Throughout this review the new phosphorus nomenclature has been used, except that "phosphono" is used rather than "dihydroxyphosphinyl" for the radical —PO_3H_2. This is in accord with the usage of *Chemical Abstracts*. Further, the compound $[PO(OR)_2]^-Na^+$ is named as a sodium dialkyl phosphite. This type of compound is prepared by the reaction between sodium and a dialkyl phosphonate, $HPO(OR)_2$. The name sodium dialkyl phosphite regards this compound as being derived from phosphorous acid, $(HO)_3P$, and is probably in accord with the actual structure of the compound. In a few cases the rules do not exactly delineate the name to be used. One such example is the compound $(C_5H_{10}N)_2POCl$, which the authors have called phosphorodipiperididic chloride, a name which is certainly within the spirit of the new rules (183).

II. Newer Methods for the Preparation of Phosphonic Acids

A. REACTION OF LITHIUM OR GRIGNARD REAGENTS WITH INORGANIC DERIVATIVES OF PHOSPHORUS

In 1950 Mikhailov and Kucherova (173) reported that a readily separable mixture of arylphosphonic and diarylphosphinic acids can be obtained by the reaction between an aryllithium reagent and phosphoropiperididic dichloride ($C_5H_{10}NPOCl_2$). This discovery was of great importance, for it was the first really new method of preparing arylphosphonic acids since the classical work of A. Michaelis at the end of the nineteenth century. In 1951 the same authors (174) modified the reaction by using phosphorodipiperididic chloride and obtained excellent yields of the arylphosphonic acids. The following reaction sequence was employed:

$$RLi + (C_5H_{10}N)_2POCl \rightarrow RPO(NC_5H_{10})_2 + LiCl$$
$$RPO(NC_5H_{10})_2 + 2H_2O \xrightarrow{HCl} RPO(OH)_2 + 2C_5H_{11}N$$

This procedure was used to prepare several new phosphonic acids derived from polynuclear hydrocarbons.

About the same time that Mikhailov and Kucherova announced their first method for preparing arylphosphonic acids, Kosolapoff (126) reported that the reaction of alkylmagnesium halides with *N*,*N*-diethylphosphoramidic dichloride could be used for preparing alkylphosphonic acids such as butylphosphonic acid.

Kosolapoff pointed out that this method cannot in general be expected to compete with the older methods for the preparation of alkylphosphonic acids but suggested that this reaction might be extended to the preparation of substituted aromatic phosphonic acids.

In 1951 Burger and Dawson (44) reported that the addition of diethyl phosphorochloridate to ortho-substituted arylmagnesium halides yields diethyl arylphosphonates, while sterically unhindered Grignard reagents form triarylphosphine oxides. It was further found that hindered or unhindered arylmagnesium halides can be converted to esters of phosphonic acids by "reverse addition," i.e., the addition of the Grignard compound to the dialkyl phosphorochloridate. They also reported that aryllithium compounds can be used in place of the Grignard reagents.

Since dialkyl arylphosphonates can be readily hydrolyzed to the corresponding phosphonic acids, the method of Burger and Dawson seems to be very convenient and has been used for preparing a considerable number of arylphosphonic acids (16, 44, 65, 130).

Independently of Burger and Dawson, Morrison (175) also discovered that Grignard reagents can be used for the preparation of arylphosphonic acids. It was found that the interaction of arylmagnesium halides and *N*,*N'*-diphenylphosphorodiamidic chloride gives fair yields of arylphosphonic dianilides. By hydrolysis of these anilides with concentrated hydrochloric acid, the corresponding phosphonic acids were obtained. No new phosphonic acids have been prepared by this procedure, which apparently has no advantages over the method of Burger and Dawson.

Morrison also noted that diphenyl arylphosphonates can be formed to a moderate extent by the addition of an aryl Grignard compound to a cooled ethereal solution of diphenyl phosphorochloridate. The free phosphonic acid can be obtained from its diphenyl ester by prolonged alkaline hydrolysis.

B. REACTION OF DIAZONIUM SALTS WITH PHOSPHORUS TRIHALIDES

The convenience of the Bart and related reactions for preparing arylarsonic and stibonic acids (103) has induced a number of investigators to attempt the preparation of arylphosphonic acids from diazonium salts. Nijk (179, p. 475) in 1922 made a determined but unsuccessful effort to prepare organophosphorus compounds by the interaction of aqueous solutions of diazonium salts and inorganic derivatives of phosphorus. Davies and Morris (64) have recorded similar unsuccessful attempts. Plets (188), on the other hand, has reported the preparation of arylphosphinic acids from diazonium salts and sodium hypophosphite. Other workers have been unable to duplicate these results (75; 127, p. 142; 146, 237, 242).

In 1951 a new general method for the preparation of arylphosphonic and diarylphosphinic acids was described (67). The method consisted in the interaction of a diazonium fluoborate and phosphorus trichloride in an anhydrous organic solvent in the presence of copper or one of its salts. The solvents used included dioxane and several aliphatic acetates. The major reaction product was usually the arylphosphonic acid; by proper choice of solvent and catalyst, a fair yield of the symmetrical phosphinic acid could also be obtained It was later discovered that phosphorus tribromide can be used in place of the trichloride (69) and that other stable diazonium salts such as the fluosilicates and the chlorozincates can be used instead of the fluoborates (78). Only in the case of *o*-nitrobenzenediazonium and *o*-toluenediazonium fluoborates has the reaction failed to produce either the expected arylphosphonic or diarylphosphinic acid (16, 67, 79). The diazo method has now been used in several laboratories for the preparation of a considerable number of new phosphonic acids and makes readily available a wide variety of organophosphorus compounds which hitherto have been difficult if not impossible to prepare (16, 24, 37, 38, 67, 68, 69, 78, 79, 84, 101, 102, 132, 133, 136).

C. REACTION OF ALKYL HALIDES WITH PHOSPHORUS TRICHLORIDE

In 1951 Clay (54) reported a new method for the preparation of alkylphosphonic acids. The method may be illustrated by the following reactions:

$$RCl + PCl_3 + AlCl_3 \rightarrow RCl \cdot PCl_3 \cdot AlCl_3 \text{ (insoluble complex)}$$
$$RCl \cdot PCl_3 \cdot AlCl_3 + 7H_2O \rightarrow AlCl_3 \cdot 6H_2O + RPOCl_2 + 2HCl$$
$$RPOCl_2 + 2H_2O \rightarrow RPO_3H_2 + 2HCl$$

The melting point of the insoluble complex is high (about 370°C. for $C_2H_5Cl \cdot PCl_3 \cdot AlCl_3$), and solutions of the complex in nitromethane conduct an electric current and produce an abnormal lowering of the freezing point. These facts suggest that the complex is ionic in character and has a structure such as $[RPCl_3]^+ [AlCl_4]^-$.

Since ethyl, isopropyl, and *tert*-butyl chlorides all yielded phosphonic dichlorides, Clay believed that this method was a general one, applicable to the alkylation of phosphorus with primary, secondary, or tertiary alkyl groups. It was soon found (120, 187), however, that the reaction of *n*-propyl, *n*-butyl, and isobutyl chloride yields isopropyl-, *sec*-butyl-, and *tert*-butylphosphonic dichloride, respectively. This type of isomerization, which is somewhat analogous to that occurring when alkyl chlorides are condensed with benzene by the Friedel–Crafts reaction, seriously limits the utility of Clay's procedure. Another complication was discovered by Crofts and Kosolapoff (62), who found that *tert*-amyl chloride yields *tert*-butylphosphonic dichloride. The elimination of a methylene group by a reaction occurring at or below room temperature seems very remarkable.

Attempts to prepare diphosphonic acids by this procedure have failed (120). Thus, 1,5-dichloropentane gives 4-chloro-1-methylbutylphosphonic dichloride and no trace of higher-boiling material. Carbon tetrachloride gives a good yield of trichloromethylphosphonic dichloride, but no diphosphonic acid (119, 120).

Kinnear and Perren have found that aliphatic ethers also react with phosphorus trichloride and aluminum trichloride to give alkylphosphonic dichlorides. The preparation of alkoxymethylphosphonic acids by the reaction between formals, phosphorus trihalides, and aluminum trichloride has been described in the patent literature (43).

D. SYNTHESIS OF AMINOALKYLPHOSPHONIC ACIDS FROM CARBONYL COMPOUNDS

Until 1952 amino-substituted alkylphosphonic acids could not be made in a single step from readily available starting materials (104). In that year Kabachnik and Medved (105) described a new synthetic method based on the reaction of aldehydes with ammonia and dialkyl phosphonates:

$$\mathrm{RCHO + NH_3 + HPO(OR')_2 \rightarrow RCH(NH_2)PO(OR')_2 + H_2O}$$

The esters of the aminophosphonic acids were isolated as hydrochlorides. Hydrolysis of these esters with hydrochloric acid yielded the free amino acids. It was soon found that ketones undergo the above reaction more readily than aldehydes (160, 161). Aliphatic ketones react most vigorously, alicyclic and mixed aliphatic-aromatic ketones react with more difficulty, while aromatic ketones react only under drastic conditions. Chalmers and Kosolapoff (47) discovered that the yields of the esters are higher if the anhydrous ammonia and the carbonyl compound are mixed before the dialkyl phosphonate is added. The free aminophosphonic acids, which are of course zwitter ions, are colorless, high-melting substances which crystallize from water with one or two molecules of solvent of crystallization.

Fields (73) has described a method of synthesizing esters of substituted aminophosphonic acids by the interaction of an aldehyde or ketone, a dialkyl phosphonate, and a primary or secondary amine. This reaction is exothermic and vigorous, and the esters can be isolated in excellent yields. However, the free aminophosphonic acids could not be prepared in pure form; generally, noncrystallizing, hygroscopic syrups were obtained.

The mechanism of the reaction discovered by Kabachnik and Medved is not clear. It has been suggested (107) that the reaction proceeds through the hydroxyphosphonates formed by the addition of the dialkyl phosphonates to the carbonyl group. If the reaction mixture is not heated, the product is in fact the hydroxyphosphonate, which can be readily converted to the amino compound by heating with ammonia. Fields (73), on the other hand, has reported that diethyl α-hydroxymethylphosphonate does *not* react with diethylamine. It seems strange that ammonia and diethylamine apparently react so differently with the hydroxy compounds.

It has also been found that Schiff bases react vigorously with dialkyl phosphonates to form esters of substituted aminophosphonic acids (73, 196, 209). This reaction is general for Schiff bases derived from both aldehydes and ketones and takes place simply upon the mixing of equimolar quantities of the two reactants.

The reactions reviewed in this section produce compounds in which both the amino group and the phosphono group are attached to the same carbon atom.

It is therefore now possible to synthesize aminophosphonic acids analogous to the biologically important α-aminocarboxylic acids.

E. PHOSPHONATION OF AROMATIC COMPOUNDS WITH PHOSPHORIC ANHYDRIDE

The first nitration of an aromatic compound was performed in 1834, when Mitscherlich prepared nitrobenzene by the action of fuming nitric acid on benzene (227). In contrast, the phosphonation of aromatic compounds by phosphoric acid or its anhydrides was unsuccessful (179, p. 473) until 1954, when it was found that benzene, chlorobenzene, *o*-xylene, and naphthalene can be phosphonated by phosphorus pentoxide at a temperature of about 275–325°C. (144, 145). The primary product of this reaction has a composition corresponding to the formula $ArHP_4O_{10}$. In some cases there are also formed secondary reaction products, which are anhydrides of the type $(ArPO_2)_n$. The primary and secondary reaction products can easily be separated, since only the latter type is soluble in the aromatic compound. For practical purposes it is not necessary to work up the insoluble and soluble reaction products separately, since both types of products can be hydrolyzed to the phosphonic acid or can be converted to the phosphonic dichloride by treatment with phosphorus pentachloride.

The phosphonation reaction produces good yields only if a large excess of the aromatic compound is used. Thus, when 20 moles of benzene was used per mole of phosphorus pentoxide (P_4O_{10}), the yield of phenylphosphonic acid was 75.5 per cent (calculated for one molecule of phenylphosphonic acid from one molecule of P_4O_{10}). When the ratio was 5 moles of benzene per mole of P_4O_{10}, the yield was only 38 per cent.

When the reaction products from chlorobenzene and phosphorus pentoxide were hydrolyzed, a mixture of chlorophenylphosphonic acids was obtained. The main component of this mixture was the para isomer, which could be obtained in a pure state by recrystallization. The other constituent, which was isolated as an *o*-toluidine salt, was probably *o*-chlorophenylphosphonic acid

The reaction between naphthalene and phosphorus pentoxide produced considerable amounts of nonphosphonated by-products, e.g., 2,2′-binaphthyl. The phosphonated compounds formed included 2-naphthylphosphonic acid and an unknown naphthalenediphosphonic acid.

During the phosphonation of *o*-xylene, considerable amounts of water-insoluble, tarry condensation products were formed. A small yield of a phosphonic acid was also isolated. The structure of this compound was not determined, but it may be 3,4-dimethylphenylphosphonic acid as suggested by the authors.

F. SYNTHESIS OF ALKYLPHOSPHONIC ACIDS FROM ALCOHOLS

Alkyl halides can be converted to alkylphosphonic acids by means of several different reactions (127, p. 121). In 1949 Chavane (49) found that alkyl derivatives other than the halides can also be used. Thus, methylphosphonic acid can be prepared from dimethyl sulfate and a sodium dialkyl phosphite. It was also found that ethylphosphonic acid can be prepared from ethyl *p*-toluenesulfonate:

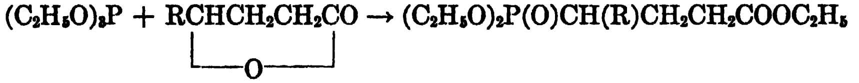
$$p\text{-}CH_3C_6H_4SO_3C_2H_5 + NaPO(OR)_2 \rightarrow p\text{-}CH_3C_6H_4SO_3Na + C_2H_5PO(OR)_2$$

$$C_2H_5PO(OR)_2 + H_2O \xrightarrow{HCl} C_2H_5PO_3H_2 + 2ROH$$

Later work (90, 178) has shown that sulfonate esters of a number of primary and secondary alcohols can be converted to phosphonic acids. This method promises to be a useful one, since the reaction conditions are mild and the alcohols used as starting materials can easily be converted to their sulfonate esters.

With *p*-toluenesulfonate esters of primary alcohols, the reaction, which is performed in tetrahydrofuran or dioxane solution, occurs smoothly at room temperature. Methanesulfonic esters react similarly except that gentle warming is required. Sulfonate esters of secondary aliphatic alcohols also react satisfactorily, but the yield of alkylphosphonate is lower than that obtained with sulfonate esters of primary alcohols. Cyclohexyl *p*-toluenesulfonate reacts only slowly, and the yield of dialkyl cyclohexylphosphonate is rather low. The *p*-toluenesulfonate esters of both phenol and *p*-nitrophenol also react with sodium diethyl phosphite. However, the course of these reactions has not been elucidated, and the products are apparently *not* derivatives of arylphosphonic acids.

The direct conversion of certain alcohols to phosphonic acids has been described in the patent literature (53). There has also been reported a reaction in which a lactone and a trialkyl phosphite react to yield the corresponding dialkyl carboalkoxy alkylphosphonate (59):



$$(C_2H_5O)_3P + \underbrace{RCHCH_2CH_2CO}_{O} \rightarrow (C_2H_5O)_2P(O)CH(R)CH_2CH_2COOC_2H_5$$

A similar reaction between lactams and phosphites has recently been described (158).

G. SYNTHESIS OF γ-OXOPHOSPHONIC ACIDS FROM MANNICH BASES

β-Dialkylaminoketones, commonly referred to as Mannich bases, are readily prepared by the treatment of ketones with formaldehyde and a secondary amine. It has recently been found (177) that heating triethyl phosphite with the methiodide of a Mannich base derived from a methyl ketone causes the ammonio group to be eliminated and produces an ester of a γ-oxophosphonic acid:

$$[RCOCH_2CH_2\overset{+}{N}(C_2H_5)_2CH_3]I^- + P(OC_2H_5)_3 \rightarrow RCOCH_2CH_2PO(OC_2H_5)_2 + [(C_2H_5)_3NCH_3]^+I^-$$

The ester can be converted by hydrolysis to the corresponding free acid. Thus, there is now available a convenient and apparently general procedure for the preparation of γ-oxoalkylphosphonic acids; another method for preparing such compounds is discussed in Section II,I.

Hydrochlorides of Mannich bases react with triethyl phosphite in a manner similar to that of the methiodides, although the yields are slightly lower and the products more difficult to purify. No reaction is observed between triethyl phosphite and the free Mannich bases. Sodium dialkyl phosphites react with both the free bases and their methiodides to produce esters of γ-oxophosphonic acids. However, the interaction of the quaternary salts and triethyl phosphite gives higher yields.

H. SYNTHESIS OF HETEROCYCLIC PHOSPHONIC ACIDS

Few compounds are known in which a phosphono or a dialkylphosphono group is attached directly to a heterocyclic ring. Kosolapoff (123) has described the preparation of diethyl acridine-9-phosphonate by the reaction between 9-chloroacridine and triethyl phosphite (the Michaelis–Arbuzov reaction). This phosphonic ester could not be obtained, however, by the interaction of 9-chloroacridine and sodium dibutyl phosphite (the Nylen reaction) Arbuzov and Lugovkin (11) have reported unsuccessful attempts to introduce the diethyl phosphono group into pyridine, but they (10) were able to prepare a number of compounds in which the diethylphosphono group is linked to oxygen heterocycles. However, the corresponding free phosphonic acids could not be obtained, since attempts at hydrolysis opened the rings.

Both the Michaelis–Arbuzov and the Nylen reactions have been tried with 2-chloro- and 2-bromopyridine, but no conversion seemed to occur (45). However, it was found that 2-chloroquinoline and 2-chlorolepidine will react with sodium dibutyl phosphite, and the resulting esters can be hydrolyzed to the corresponding free acids. By contrast, 2-chloro-4,8-dimethylquinoline could not be converted to a phosphonic ester by the Nylen reaction.

The preparation of two phosphonic acid derivatives of dihydrocoumarin has recently been described (14). These compounds were synthesized by the method of Pudovik, which is reviewed in the next section.

I. MISCELLANEOUS METHODS

A considerable number of organophosphorus compounds have been prepared by the addition of dialkyl phosphonates to ethylenic double bonds conjugated with certain "activating" groups. These groups include the dialkylphosphono (141, 193, 202, 206, 207, 217, 222), oxo (35, 36, 140, 192, 194, 198, 203, 204, 212), cyano (35, 36, 199, 203, 205, 213), carboalkoxy (35, 36, 195, 197, 199, 200, 203, 205, 213), carbamyl (199), and carboxy (199) groups. This method was first described by Pudovik but was discovered independently in a number of other laboratories. The dialkyl alkylphosphonates obtained by this reaction are usually colorless, viscous, high-boiling liquids, which can be obtained in good yields and hydrolyzed to give the corresponding phosphonic acids. The addition reaction is exothermic and is promoted by basic catalysts, especially sodium dialkyl phosphites and sodium alkoxides. Alkyl groups attached to the vinyl radical generally inhibit the addition of the dialkyl phosphonate, and the reaction then requires larger amounts of the basic catalyst. The addition occurs in a direction contrary to Markownikoff's rule and thus resembles the Michael type of reaction. Unsaturated aldehydes first combine with the dialkyl phosphonates at the carbonyl group to form α-hydroxyphosphonic esters (208), while unsaturated ketones first react at the carbon–carbon double bond to form keto phosphonic esters (194). If an excess of the dialkyl phosphonate is used, unsaturated aldehydes and ketones yield hydroxydiphosphonic esters. Addition reactions have been carried out also with compounds containing activated acetylenic bonds (199, 213). In this case two moles of the dialkyl phosphonate add to the triple bond to form a diphosphonic ester, regardless of whether the reagents are used in equimolar or other proportions.

Closely related to the reactions discussed above is the peroxide-catalyzed addition of diethyl phosphonate to an enol ester (191). Hydrolysis of the addition product yields a β-hydroxyphosphonic acid. The addition of phosphine to olefins is also catalyzed by peroxides as well as by ultraviolet light (20, 42, 229) and by strong non-oxidizing acids (42). The free-radical-initiated reaction yields mixtures of primary, secondary, and tertiary phosphines. The primary phosphines can be separated from the mixtures by fractional distillation and can be oxidized to the corresponding phosphonic acids with nitric acid or 30 per cent hydrogen peroxide. The acid-catalyzed addition reaction yields mainly primary phosphine, a little secondary phosphine, and no tertiary phosphine. Alkylphosphines can be prepared also by the interaction of olefins, white phosphorus, and hydrogen at a temperature above 200°C. and under a pressure of 700–3000 atm. (181).

The use of diazoalkanes for the preparation of organophosphorus compounds has been recently reviewed (226).

Phosphonic acids have been synthesized by the interaction of yellow phosphorus and alkyl or aryl halides, but this procedure seems to have little preparative importance (137).

III. REACTIONS OF PHOSPHONIC ACIDS

A. ACID DISSOCIATION CONSTANTS

1. *Aliphatic and alicyclic phosphonic acids*

Although it has been known for a long time that phosphonic acids are moderately strong and dibasic, no information concerning their dissociation constants was available until 1930, when Nylen (180) reported the pK values of several alkylphosphonic acids. Later workers have determined the acidity constants of a considerable number of phosphonic acids. The recorded acid dissociation constants of unsubstituted alkylphosphonic acids are collected in table 1. These acids are weaker than phosphoric acid (pK_1 = 1.97; pK_2 = 6.82) and its monoalkyl esters (139). The pK values of the phosphonic acids increase with an increase in the number of carbon atoms in the alkyl group and with the degree of branching of the carbon chain. This effect is obviously due to the electron-repelling characteristics of the saturated carbon atom. The median difference between the first and second pK's of the alkylphosphonic acids is 5.62 units. The equation used by Branch and Calvin (39) for calculating the dissociation constants of nonresonating acids predicts a pK difference of 4.9.

The recorded dissociation constants of substituted aliphatic phosphonic acids are collected in table 2. The symbol pK_1 used in tables 1 and 2 refers to the first dissociation constant of the phosphono group, i.e., to the equilibrium constant of the reaction:

$$RPO_3H_2 \rightleftharpoons H^+ + RPO_3H^-$$

Similarly, the symbol pK_2 refers to the reaction:

$$RPO_3H^- \rightleftharpoons H^+ + RPO_3^{--}$$

The acid dissociation constants of other functional groups (e.g., COOH and NH_3^+) are not given in table 2; in many cases, however, they have been determined and can be found in the references. There appears to be no ambiguity about the assignments of the experimental pK values to given acid functions. The last pK's of the aminoalkylphosphonic acids range from 10.0 to 11.25 and, accordingly, have been assigned to the ammonio group. The first pK obtained by titration of 3-anilinopropylphosphonic acid, $C_6H_5NH_2^+(CH_2)_3PO_3H^-$, with alkali is 4.25; this value is undoubtedly the pK_a of the substituted anilinium group. Since the pK_a of N-propylanilinium ion is 5.05, the PO_3H^- group of 3-anilinopropylphosphonic acid must be acid-strengthening and hence electron-attracting. The median of the pK_2 − pK_1 values listed in table 2 is 5.05. This

TABLE 1

Acid dissociation constants of alkylphosphonic acids

Alkyl Group	pK_1	pK_2	pK_2 − pK_1	References
Methyl	2.33	7.76	5.43	(180)
	2.35	7.1	4.75	(52, 218)
	2.38	7.74	5.36	(62)
	2.48	7.34	4.86	(30)
Ethyl	2.39	7.98	5.59	(180)
	2.45	7.85	5.40	(52, 218)
	2.43	8.05	5.62	(62)
n-Propyl	2.45	8.06	5.61	(180)
	2.49	8.18	5.69	(62)
Isopropyl	2.55	7.75	5.20	(52)
	2.66	8.44	5.78	(62)
n-Butyl	2.59	8.19	5.60	(62)
Isobutyl	2.70	8.43	5.73	(62)
s-Butyl	2.74	8.48	5.74	(62)
t-Butyl	2.79	8.88	6.09	(62)
Neopentyl	2.84	8.65	5.81	(62)
1,1-Dimethylpropyl	2.88	8.96	6.08	(62)
n-Hexyl	2.6	7.9	5.3	(52, 218)
	2.4	8.25	5.85	(148)
n-Dodecyl	*	8.25	—	(52, 218)
	4.22†	9.81†	5.59	(246)

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* The first pK was not determined because of the low solubility of this compound in acid solutions.

† These values are on the molal scale and were obtained in 50 per cent by weight ethanol.

TABLE 2

Acid dissociation constants of substituted aliphatic phosphonic acids

RPO_3H_2 R =	pK_1	pK_2	pK_2 − pK_1	References
$CH_3(CH_2)_5CH(COOH)$	1	—	—	(52)
CF_3	1.16	3.93	2.77	(30)
CCl_3	1.63	4.81	3.18	(63)
$NH_3^+CH_2$	2.35*	5.9	3.55	(218)
	1.85*	5.35	3.50	(48, 52)
$(^-OOCCH_2)_2NH^+CH_2$	—	5.57	—	(221)
$CHCl_2$	1.14	5.61	4.47	(63)
CH_2Cl	1.40	6.30	4.90	(63)
CH_2Br	1.14	6.52	5.38	(63)
$(^-OOCCH_2)_2NH^+(CH_2)_2$	—	6.54	—	(221)
CH_2I	1.30	6.72	5.42	(63)
$NH_3^+CH_2CH_2$	2.45*	7.00	4.55	(52, 218)
$C_6H_5CH{=}CH$	2.00	7.1	5.10	(52)
$HOCH_2$	1.91	7.15	5.24	(63)
$C_6H_5NH_2^+(CH_2)_3$	2.1*	—	—	(218)
$C_6H_5NH(CH_2)_3$	—	7.17	—	(218)
$Br(CH_2)_3$	2.25	7.3	5.05	(52)
$CH_3(CH_2)_5CH(COO^-)$	—	7.5	—	(52)
$C_6H_5CH_2$	2.3	7.55	5.25	(52)
	1.85	7.4	5.55	(148)
$NH_3^+(CH_2)_4$	2.55*	7.55	5.00	(52, 218)
$NH_3^+(CH_2)_5$	2.6*	7.6	5.0	(218)
	2.6*	7.65	5.05	(52)
$NH_3^+(CH_2)_{10}$	†	8.00	—	(52, 218)
$^-OOC(CH_2)_{10}$	—	8.25	—	(52)
$(CH_3)_3SiCH_2$	3.22	8.70	5.48	(118)
$C_6H_5CH_2$	3.3‡	8.4‡	5.1	(52)
$(C_6H_5)_3C$	3.85‡	9.00‡	5.15	(52)

* Determined by titration of the aminophosphonic acid with hydrochloric acid.

† The first pK was not determined because of the low solubility of this compound in acid solutions.

‡ These values were obtained in 50 per cent ethanol.

is close to the theoretical value of 4.9; however, the stronger acids in table 2 tend to have pK_2 − pK_1 values which are considerably lower than the median value.

The pK values of several alicyclic phosphonic acids also have been measured. Cyclohexylphosphonic acid was first prepared by Clayton and Jensen (55) by the chlorophosphonation of cyclohexane. The acid was reported to melt at 166–167°C. and have dissociation constants of 4×10^{-5} and 2×10^{-10}. Since these dissociation constants differ considerably from those of hexylphosphonic acid, some doubt existed concerning the identity of the acid prepared by Clayton and Jensen. Accordingly, Lesfauries and Rumpf (146, 148, 237) repeated the chlorophosphonation of cyclohexane and obtained an acid with a melting point of 168°C. and pK values of 2.2 and 8.35. Subsequent to this work cyclohexylphosphonic acid was prepared in several laboratories by a number of different methods (72, 82, 88, 178, 229). There is now no doubt whatever that the chlorophosphonation reaction *does* yield cyclohexylphosphonic acid. However, the acid dissociation constants reported by Clayton and Jensen must be in error, since the first ionizable hydrogen of cyclohexylphosphonic acid can be titrated stoichiometrically with the aid of methyl purple (endpoint at pH 5.4) (82). The dissociation constants reported by Lesfauries and Rumpf for cyclohexylphosphonic acid seem quite reasonable. The preparation and pK values of a tetrahydronaphthylphosphonic acid and a decahydronaphthylphosphonic acid obtained by the chlorophosphonation of tetralin and decalin, respectively, were reported. The phosphonic acid prepared from decalin was presumably a mixture, but gave a titration curve like that of a pure dibasic acid with pK values of 2.5 and 8.2. Tetralin yielded, apparently, a single derivative (m.p. 209°C.) with pK values of 2.0 and 8.0. The PO_3H_2 group is probably in the 2-position, since the tetrahydronaphthylphosphonic acid, although stronger than the acids derived from hexane, cyclohexane, or decalin, is weaker than phenylmethylphosphonic acid. Therefore, the acid-strengthening effect of the aromatic ring (32) is presumably further removed from the PO_3H_2 group than in the case of phenylmethylphosphonic acid.

The pK values of several diphosphonic acids have been measured and are listed in table 3. These acids dissociate according to the following scheme:

$$\text{-R—PO}_3\text{H}_2 \overset{K_1}{\rightleftharpoons} \text{H}^+ + (\text{H}_2\text{O}_3\text{P—R—PO}_3\text{H})^-$$

$$(\text{H}_2\text{O}_3\text{P—R—PO}_3\text{H})^- \overset{K_2}{\rightleftharpoons} \text{H}^+ + (\text{HO}_3\text{P—R—PO}_3\text{H})^{--}$$

$$(\text{HO}_3\text{P—R—PO}_3\text{H})^{--} \overset{K_3}{\rightleftharpoons} \text{H}^+ + (\text{HO}_3\text{P—R—PO}_3)^{-3}$$

$$(\text{HO}_3\text{P—R—PO}_3)^{-3} \overset{K_4}{\rightleftharpoons} \text{H}^+ + (\text{O}_3\text{P—R—PO}_3)^{-4}$$

It is seen from table 3 that the values of both pK_2 and pK_3 decrease as the distance between the phosphorus atoms becomes smaller. This generalization can be explained by the conclusion that the PO_3H^- group, which is a constant substituent in equilibria 2 and 3, is electron-attracting and consequently acid-strengthening. By contrast the value of the pK_4 tends to *increase* as the distance between the phosphorus atoms becomes smaller. The acidity of the last ionizable hydrogen must therefore be weakened by the PO_3^{--} group, which must, accordingly, have an electron-repelling inductive effect.

The dissociation constants of a tetraphosphonic acid, ethylenebis(nitrilodimethylene)tetraphosphonic acid, have recently been reported (245). The eight pK values were found to be 1.46, 2.72, 5.05, 6.18, 6.63, 7.43, 9.22, and 10.95.

The dissociation constants discussed in this section were determined by

TABLE 3

Acid dissociation constants of aliphatic diphosphonic acids

Compound	pK_1	pK_2	pK_3	pK_4	References
$H_2O_3P(CH_2)_4PO_3H_2$	<2	2.75	7.54	8.38	(223)
$H_2O_3P(CH_2)_3PO_3H_2$	<2	2.65	7.34	8.35	(223)
$H_2O_3PCH_2CH(CH_3)PO_3H_2$	<2	2.6	7.00	9.27	(222)
$H_2O_3PCH_2PO_3H_2$	<2	2.57	6.87	10.33	(223)

potentiometric titration. No activity corrections were made, nor were liquid-junction potentials estimated. Hence the experimental results are nonthermodynamic or "apparent" dissociation constants. In some of the papers it is not clear whether the reported pK values have been calculated by means of the appropriate equations (87) or are merely the pH values at the midpoints of the titration curves. This uncertainty does not affect the values given for the second dissociation constants of the PO_3H_2 group, but the values given for the first dissociation constants may be considerably in error if the midpoint pH's were assumed equal to the pK's.

Since the last pK's of many of the aliphatic and alicyclic phosphonic acids are greater than 8, none of the commonly used indicators can be relied upon for determining the neutral equivalents of these acids. Thymolphthalein, which changes from colorless to blue at about pH 9.3, can probably be used for many of the aliphatic phosphonic acids with strongly electron-attracting substituents.

2. Arylphosphonic acids

The first measurements of the acid dissociation constants of arylphosphonic acids were performed by Lesfauries and Rumpf (146, 147, 237), who reported the pK values of several phosphonic acids and concluded that the effects of substituents on the acidity of benzoic acid and of phenylphosphonic acid are very similar. This conclusion suggests that the Hammett equation (91) applies to the acid dissociation constants of arylphosphonic acids and that the reaction constants (ρ) for both series of acids are approximately the same. The correctness of these suggestions was demonstrated by later workers (101), who determined the dissociation constants of twenty-five meta- and para-substituted arylphosphonic acids by potentiometric titration in water and 50 per cent

TABLE 4

Reaction constants (ρ) for the acid dissociation of arylphosphonic acids of the type 2-X-4(or 5)-$RC_6H_3PO_3H_2$

	Solvent			n†	−log k°‡	References
		$—PO_3H_2 \rightleftharpoons H^+ + —PO_3H^-$				
H	H_2O	0.755	0.030	10	1.84	(101)
Cl Br	H_2O	0.749	0.090	3	1.70	(102)
H	50% C_2H_5OH	0.986	0.059	12	3.13	(101)
Cl, Br	50% C_2H_5OH	0.995	0.031	4	2.94	(102)
		$—PO_3H^- \rightleftharpoons H^+ + —PO_3^{--}$				
H	H_2O	0.949	0.058	12	6.97	(101)
Cl, Br	H_2O	0.908	0.152	6	6.90	(102)
CH_3O	H_2O	0.881	0.105	3	7.69	(102)
H	50% C_2H_5OH	0.991	0.063	12	8.23	(101)
Cl, Br	50% C_2H_5OH	1.191	0.033	5	8.25	(102)
CH_3O	50% C_2H_5OH	1.108	0.057	3	8.82	(102)

* The standard deviation from the best straight line.

† The number of compounds on which the calculation of ρ is based.

‡ The intercept of the plot of σ vs. —log K.

TABLE 5

Substituent constants of the phosphono anions

Substituent		
PO_3H^-	0.25,* 0.24†	0.17,* 0.29†
PO_3^{--}	−0.02‡	−0.16‡

* Calculated from the acid dissociation constants, in water, of the carboxy group of *m*- and *p*-carboxyphenylphosphonic acids.

† Calculated from the acid dissociation constants, in 50% ethanol, of the carboxy group of *m*- and *p*-carboxyphenylphosphonic acids.

‡ Calculated from the acid dissociation constants, in water, of the hydroxy group of *m*- and *p*-hydroxyphenylphosphonic acids.

ethanol. Reaction constants (ρ) calculated from these data are included in table 4. Several of the arylphosphonic acids used in this investigation contain substituents which are acid functions. The p*K* values of these functions were determined and used to calculate the substituent constants (σ) of the PO_3H^- and PO_3^{--} groups. These values, which are listed in table 5, indicate that the PO_3H^- group is electron-attracting and that the PO_3^{--} group is electron-repelling. Similar conclusions were reached by Schwarzenbach and Zurc (223) in their study of the p*K*'s of aliphatic diphosphonic acids.

The p*K* values of a considerable number of *o*-substituted arylphosphonic acids have also been measured and are listed in table 6. Although the Hammett equation does not apply to ortho substituents, it can be used for the effect of substituents (R) on the reactivity of side chains (Y) in series of compounds of the type 2-X-4(or 5)-RC_6H_3Y, if the ortho substituent (X) is constant throughout the series (97, 98, 216). Some of the compounds listed in table 6 can be grouped into two such series with X = Cl (or Br) and CH_3O. The justification for combining compounds with *o*-chloro and *o*-bromo substituents into a single series depends on the fact that both substituents equally affect the p*K* of phenylphosphonic acid and that reaction constants are insensitive to the nature of the ortho substituent (X). Reaction constants for the two series are included in table 4. Many of the ortho-substituted acids have p*K*'s which differ significantly from the p*K*'s of the corresponding para isomers. In a few cases these differences can be explained by the assumption that the inductive effect from the ortho position is somewhat larger than from the para position. Most of the "ortho effects", however, are probably due to intramolecular hydrogen bonding and can be elucidated by mechanisms discussed in detail in reference 102.

The dissociation constants reviewed above were determined by potentiometric measurements of cells containing liquid junctions. The ionic strengths of the solutions used were about 0.1, but no attempt was made to keep the ionic strength constant during a determination. The acid dissociation constants of phenylphosphonic acid at a constant ionic strength of 1.0 have been determined by both potentiometric and spectroscopic methods (17, p. 428). A recent paper describes the measurement by a spectroscopic method of the dissociation constants in water of several para-substituted phenylphosphonic acids (189). In

TABLE 6

Acid dissociation constants of the ortho-substituted arylphosphonic acids

$2\text{-X-RC}_6\text{H}_3\text{PO}_3\text{H}_2$		$\text{p}K_{\text{PO}_3\text{H}_2}$		$\text{p}K_{\text{PO}_3\text{H}^-}$		References
X	R	In H_2O	In 50% C_2H_5OH	In H_2O	In 50% C_2H_5OH	
Cl	4-O_2N	1.12	2.18	6.14	7.31	(102)
Br	5-O_2N	(a)	(a)	6.14	7.47	(102)
Cl	5-Cl	(a)	2.55	6.63	7.84	(102)
Cl	H	1.63	2.94	6.98	8.21	(102)
Br	H	1.64	2.91	7.00	8.22	(102)
Br	5-CH_3	1.81	3.04	7.15	8.35	(102)
Cl	4-NH_2	—	—	7.33	(a)	(102)
CH_3O	4-O_2N	1.53	2.61	6.96	7.94	(102)
CH_3O	H	2.16	3.62	7.77	8.87	(102)
CH_3O	4-NH_2	—	—	8.22	9.53	(102)
HO[b]	4-O_2N	1.22	1.95	5.39	6.59	(102)
O_2N	H	1.45	—	6.74	—	(80)
F	H	1.64	2.84	6.80	7.99	(102)
I	H	1.74	3.06	7.06	8.40	(102)
NH_2[c]	H	—	—	7.29	8.34	(102)
CH_3	H	2.10	—	7.68	—	(16)
C_6H_5	H	(a)	3.78	8.13	(d)	(102)
HOOC[e]	H	1.71	2.47	9.17[f]	10.03[f]	(102)

[a] The compound was not sufficiently soluble.

[b] $\text{pH}_{\text{OH}} > 12$ in water; > 13 in 50% ethanol.

[c] $\text{p}K_{\text{NH}_3^+} = 4.10$ in water.

[d] The sodium salt precipitated during titration.

[e] $\text{p}K_{\text{COOH}} = 3.78$ in H_2O and 4.89 in 50% ethanol.

[f] The substituent is actually COO^-.

neither this study nor the earlier studies were activity corrections or liquid-junction potentials estimated; hence all the reported p*K*'s are nonthermodynamic values.

The neutral equivalents of practically all arylphosphonic acids which do not have interfering acid functional groups (i.e., groups such as SO_2NH_2 and OH, the p*K*'s of which are near 9) can be determined by titration in aqueous or alcoholic solution with thymolphthalein as an indicator (102). Only three exceptions to this rule have been found: namely, *o*-carboxyphenylphosphonic acid, 2-methoxy-4-aminophenylphosphonic acid, and 2-biphenylylphosphonic acid. The last p*K* values of these acids in water are greater than 8.1. The weakest arylphosphonic acid which has given a theoretical neutral equivalent with thymolphthalein is *o*-methoxyphenylphosphonic acid, which has a second p*K* in water of 7.77.

B. SALTS OF PHOSPHONIC ACIDS

Phosphonic acids, being dibasic, form both acid and neutral salts, often occurring with water of crystallization. Many of these salts are insoluble in water and have been used since the earliest days of organic phosphorus chemistry for the isolation and purification of phosphonic acids (93, 171). However, because salts of phosphonic acids vary widely in their solubility it is difficult to generalize as to the best salt to use for the isolation of any particular phosphonic acid.

Ammonium salts and salts of the alkali metals are usually very soluble in water, although the monosodium salt of 2-phosphonoöctanoic acid is only slightly soluble (49, p. 361). They are customarily prepared by evaporation of half-neutralized or neutralized solutions of the acids (166). Freeze-drying methods have recently been used for isolating water-soluble salts of phosphonic acids (30, 71). Dipotassium 9-(9-phenyl)fluorenyl- and (phenyl di-*p*-tolyl)methylphosphonates have been obtained from the corresponding acids by crystallization from aqueous potassium hydroxide (92). Many of the water-soluble alkali metal salts can be recrystallized from alcohol. The dipotassium salt of D-glucopyranose-6-deoxy-6-phosphonic acid precipitates from methanol solution when the corresponding tetraacetyl compound is hydrolyzed with potassium methoxide (90). Several alkali metal salts have been characterized by means of their infrared spectra (30, 71).

The lithium salts of a wide variety of phosphonic acids have been added to lithium base greases (46). The claim is made that the resulting greases have greater mechanical stability and resistance to shear during working or milling. There is also less tendency for separation of oil from the grease during storage. The most satisfactory additives have been the dilithium salts of 2-ethylhexyl-, tetradecyl-, octadecyl-, and phenylphosphonic acids.

Heavy metal salts in particular have been useful for the isolation and purification of soluble phosphonic acids. The salt most frequently used has been the lead salt (137, 156, 221). In several cases phosphonic acids have been isolated only as the lead salts (57). Silver salts (214) have also been used for isolating phosphonic acids; however, disilver trichloromethylphosphonate explodes on slight heating in the dry state (250).

Calcium and barium salts have frequently been used for the isolation of phosphonic acids. Many such salts are more soluble in cold water than in hot (190). The barium and calcium salts of different phosphonic acids vary widely in their solubility in water. Barium trifluoromethylphosphonate is sparingly soluble; the lead, silver, mercurous, and calcium salts of this acid, however, are apparently soluble (30). This varying solubility has been used for the separation of a mixture of two phosphonic acids, one of whose barium salts is soluble while the other is insoluble in water (171, p. 276).

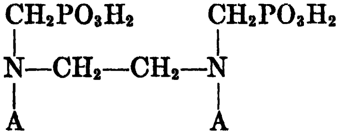
Magnesium salts of phosphonic acids have been more thoroughly investigated than other metallic phosphonates. It has long been known that the magnesium salts of aromatic arsonic acids are precipitated only on heating, whereas the inorganic salt (magnesium ammonium arsenate) precipitates in the cold. This phenomenon has frequently been used for the separation of inorganic from organic arsenic acids. That a similar phenomenon occurs with phosphonic and phosphoric acids was suggested by Bauer (22) when phosphanilic acid was found to give a magnesium salt which precipitated from hot water. The magnesium salt technique has also been used for the separation of phosphate ion from a phosphonic acid (57). The magnesium salts of aromatic phosphonic acids have recently been the subject of a more comprehensive examination (80). It was shown that in a large series of acids only two acids gave insoluble magnesium salts in the cold.

All para-substituted and all but one meta-substituted acid gave copious precipitates when heated with magnesia mixture. *o*-Methyl-, *o*-amino-, *o*-hydroxy-, and *o*-fluorophenylphosphonic acids gave sparse precipitates when heated with magnesia mixture; all other ortho-substituted acids failed to give an insoluble magnesium salt. This difference between ortho-substituted and the meta- and para-substituted phosphonic acids was then used as the basis for the separation of *o*-nitrophenylphosphonic acid from its meta isomer; the ortho isomer was thus prepared in a pure state for the first time. It seems probable that this technique could be used for separating other ortho isomers from mixtures of isomeric phosphonic acids.

It has been suggested that thallous salts might prove useful for the characterization of phosphonic acids (86). Both thallous hydrogen and dithallous phenylphosphonate were prepared and found to melt at 200–201°C. and 317–320°C., respectively. It would seem probable that the melting points of thallous salts of most substituted aromatic phosphonic acids would be too high to be of value for characterizing these acids. It should be noted that thallous formate and ammonia give a precipitate of thallous phosphate with orthophosphoric acid; no precipitate is obtained with phenylphosphonic acid (145).

The use of phenylphosphonic acid as a reagent for the quantitative determination of thorium has been recommended (17). Phenylphosphonic acid precipitates thorium quantitatively from solution at pH values of 0.5 and above. The resulting salt, $Th(C_6H_5PO_3)_2 \cdot 3H_2O$, is stable to 240°C.; above this temperature one mole of water is lost.

Compounds containing phosphonic acid groups have been prepared as chelating agents for metal ions. Closely related to ethylenediaminetetraacetic acid (Versene) is a group of compounds of the type shown in formula I,



$$\begin{array}{ccc} CH_2PO_3H_2 & & CH_2PO_3H_2 \\ | & & | \\ N & -CH_2-CH_2- & N \\ | & & | \\ A & & A \end{array}$$

I

where A may be a $—CH_2PO_3H_2$ group, a $—CH_2COOH$ group, or a hydrogen atom (33, 34, 245). These compounds are used in the form of their alkali metal salts to chelate with a wide variety of heavy metal ions, forming complexes in which the ionic properties of the metal ion are greatly suppressed.

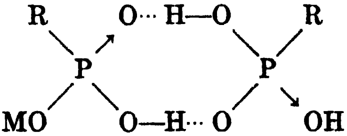
A similar chelating agent, bis(carboxymethyl)aminomethylphosphonic acid, has been prepared by condensing chloromethylphosphonic acid with iminodiacetic acid (221). Calcium, magnesium, strontium, and barium ions have been found to chelate with this compound.

Salts with aromatic amines have been used for the isolation, purification, and characterization of phosphonic acids, but again the type of salt produced varies with the acid used. Bromomethyl- and chloromethylphosphonic acids form the monoanilinum salt (249, 252) even when an excess of aniline is used, whereas trichloromethylphosphonic acid forms both mono- and dianilinium salts (248, 250). The neutral salt, however, loses a mole of aniline on storage or recrystallization to form the acid salt (250). Anilinium hydrogen chloromethylphosphonate, m.p. 199–200°C., has been used for characterizing the acid (120). Bengelsdorf and Barron (29) obtained this salt, as well as other monoamine salts of chloromethylphosphonic acid, by addition of the amine to a benzene solution of the free acid. *p*-Toluidine, however, gave an equimolar mixture of the mono- and di-salts. *o*-Phenylenediamine gave a salt with a molar ratio of amine to acid of 2:1, whereas the corresponding para isomer gave a salt with a ratio of amine to acid of 1:1. These authors suggest that, since salts of phosphonic acids with weakly basic aromatic amines can be readily titrated with standard alkali to give reproducible neutralization equivalents, these salts may well prove to be valuable for characterization of the acids. Since all but one of the amine salts of trichloromethylphosphonic acid melted with decomposition at temperatures above 200°C., the melting points of these salts are not of value for characterization purposes. Trifluoromethylphosphonic acid also gave both mono- and dianilinium salts which decompose without melting when heated; they were characterized by means of their infrared spectra (71).

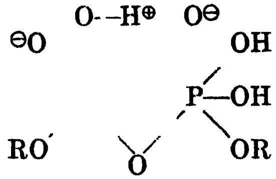
The precipitation of phosphonic acids as their *p*-toluidine salts has been suggested as a desirable method for the isolation of the acids from complex reaction mixtures (38). The *p*-toluidine salts of a series of aromatic phosphonic acids were obtained, some as the pure neutral salt, others as a mixture of mono- and di-salts. Where the free acid was required, the *p*-toluidine salt was dissolved in sodium hydroxide, the toluidine removed by steam distillation, and the sodium ion removed in an ion-exchange column. The resulting solution was then evaporated to incipient crystallization in order to obtain the free acid. Although this method undoubtedly gives good results with certain phosphonic acids, the present authors have experienced difficulties when the acids were very soluble. Our difficulties have arisen from the fact that phosphoric acid also gives an insoluble *p*-toluidine salt. Since crude reaction mixtures from the synthesis of phosphonic acids often contain phosphoric acid, the isolation of soluble phosphonic acids is not readily accomplished by this method.

In addition to the expected mono- and di-salts, phosphonic acids also form a series of hemi-salts of the general formula $RPO_3HM \cdot RPO_3H_2$, where M is usually sodium or potassium. Although these hemi-salts were first observed by Michaelis (172, p. 226), they were not used extensively until recent years. It has been discovered that the hemi-sodium or hemi-potassium salts of aromatic phosphonic acids are usually less soluble in water than the free acids and hence precipitate from solution when an alkaline solution of the acid is acidified to Congo red (67, 144). This fact has been used extensively as a means of isolating the acids from complex reaction mixtures and is probably the best means of obtaining the acids under many circumstances. The fact that a hemi-alkali salt may be obtained when an alkaline solution of the acid is acidified has been overlooked by various authors; it is quite probable that many compounds described as hydrated free acids or as acid salts are in reality the hemi-alkali salts (15, 155). A determination of the neutral equivalent would distinguish between these possibilities.

The structure of the hemi-salts has not been established with certainty. Kosolapoff (129) has performed experiments designed to elucidate the structure of these and other salts of phosphonic acids; the results are discussed in the section on molecular weights. Although the exact formulation of the steps involved in the progressive neutralization of phosphonic acids is a matter of opinion, the structure (II) proposed for the hemi-salts may well be correct.


II

Friedman and Seligman (85) have suggested structure III and various resonance hybrids of this structure for the "half-salts" of naphthyl acid phosphates. These "half-salts" of naphthyl acid phosphates are undoubtedly analogous to the hemi-salts of the phosphonic acids. In all of the structures proposed by Friedman and Seligman one phosphorus atom is bonded to five oxygen atoms. Similar structures for other phosphorus compounds have been justifiably criticized by other workers (184, 185); the present evidence does not seem to warrant analogous structures for the hemi-salts of phosphonic acids.


III

C. PROBLEMS OF ORIENTATION IN ARYLPHOSPHONIC ACIDS

1. *Nitration*

Phenylphosphonic acid was first nitrated in 1875 with fuming nitric acid in a sealed tube (169). The nitrophenylphosphonic acid, which was isolated by a tedious procedure involving the barium salt, was believed to be a single isomer (170, 171). However, no information about the position of the nitro group was obtained. The melting point was first (169) reported to be 140°C., but in other papers (170, 171) it was given as 132°C. In 1922 the nitration of phenylphosphonic acid was reinvestigated by Nijk (179, p. 464), who showed that *m*-nitrophenylphosphonic acid is formed; the presence of either ortho or para isomers was not detected. Hence, it seemed that the sample of nitrophenylphosphonic acid which melted at 140°C. was the pure meta isomer. This conclusion was accepted without question for a long time, and the nitrophenylphosphonic acid obtained by Nijk's procedure has been used whenever the *m*-nitro compound was desired (124). In 1949, however, evidence was presented (125) that the material melting at 140°C. was not a single compound but contained, in addition to *m*-nitrophenylphosphonic acid, a considerable proportion of either the ortho or the para isomer. This possibility was strengthened by the later observation that pure *m*-nitrophenylphosphonic acid (prepared from *m*-nitrobenzenediazoniumfluoborate) has a melting point of 155–156°C. (67). Finally, both *o*-nitro- and *m*-nitrophenylphosphonic acids were isolated from the mixture of isomers obtained by nitrating phenylphosphonic acid (80). It is now obvious that phenylphosphonic acid does *not* undergo nitration exclusively in the meta position, although the meta isomer predominates.

The literature also contains descriptions of nitro compounds prepared by the nitration of *p*-chlorophenylphosphonic acid (37; 168, p. 230; 179, p. 471), *p*-bromophenylphosphonic acid (24; 168, p. 243), *p*-tolylphosphonic acid (168, pp. 270, 273), *o*-tolylphosphonic acid (168, p. 298), *p*-methoxyphenylphosphonic acid (24; 168, p. 254), 2,4-dimethylphenylphosphonic acid (243, p. 1722), 2,5-dimethylphenylphosphonic acid (244), and 3-chloro-4-methylphenylphosphonic acid (164). In these cases it has been assumed that the nitro group enters meta to the phosphono group. This assumption is, of course, very reasonable but no unequivocal proof of the structure or purity of any of these nitrated products has been reported. Nitration products of 3,5-dimethylphenylphosphonic acid (243, p. 1723) and *m*-ethoxycarbonylaminophenylphosphonic acid (179, p. 479) have also been described, in these cases the nitro group probably entered either the 2- or the 4-position.

2. The Friedel–Crafts reaction

The Friedel–Crafts reaction has been long used for the preparation of phosphonic acid derivatives of aromatic compounds. A serious disadvantage of this method is that mixtures of arylphosphonic acids are sometimes obtained, which are in general very difficult to separate. Furthermore, it is necessary to establish the position occupied by the phosphono group relative to other substituents in the benzene ring. Some of the structural problems that have arisen concerning arylphosphonic acids prepared by the Friedel–Crafts reaction are discussed below.

The Friedel–Crafts reaction between phosphorus trichloride and toluene was first described in 1879 by Michaelis (167), who isolated *p*-tolylphosphonic acid and determined its structure. It was later suggested that the ortho isomer may also be formed in this reaction (172, p. 210). Recently, Kosolapoff (130) has isolated *o*-tolyl-, *m*-tolyl-, and *p*-tolylphosphonic acids in the ratio 10:27:63 from a mixture of isomeric acids obtained through the Friedel–Crafts reaction. It is possible that other alkylbenzenes behave analogously to toluene. Thus, from 0.5 mole of ethylbenzene were obtained 35 g. of *p*-ethylphenylphosphonic acid (m.p. 174.5–175.0°C.) and 4 g. of another phosphonic acid, m.p. 116–117°C. Kosolapoff suggested that the latter acid might be the meta isomer. However, it is now known that the meta isomer melts at 128–129.5°C. and that the ortho isomer melts at 145.5–147°C. (79). It seems probable, therefore, that the low-melting material reported by Kosolapoff was a mixture of isomeric ethylphenylphosphonic acids.

In 1929 Lindner and Strecker (150) subjected naphthalene to the Friedel–Crafts reaction and obtained a naphthylphosphonic acid which melted at 188–189°C. and gave no significant melting-point depression with authentic 2-naphthylphosphonic acid (m.p. 193–194°C.). On the basis of other evidence, however, Lindner and Strecker were led to believe that the phosphonic acid obtained in the Friedel–Crafts reaction was the 1-isomer. This conclusion was generally accepted until 1953, when it was definitely established that the reaction between naphthalene and phosphorus trichloride yields the pure 2-isomer (242, p. 1318).

From a Friedel–Crafts reaction between bromobenzene and phosphorus trichloride Michaelis (168, p. 244) isolated *p*-bromophenylphosphonic acid and an acidic material (m.p. 265°C.) which was presumed to be an isomeric bromophenylphosphonic acid. This inference cannot be correct, for the melting points of *o*-bromophenyl-, *m*-bromophenyl-, and *p*-bromophenylphosphonic acid are all below 265°C. Since the unknown compound was precipitated from ammoniacal solution by the addition of hydrochloric acid, it seems possible that this unidentified material was the hemi-ammonium salt of a bromophenylphosphonic acid.

D. THE DYE AND INDICATOR PROPERTIES OF PHOSPHONIC ACIDS

Relatively few dyes have been prepared which contain phosphonic acid groups. This may be due to the paucity in the past of good methods for preparing such compounds. With the better synthetic methods which have been developed in recent years the number of dyes containing phosphonic acid groups will probably increase.

In 1952 Klotz, Burkhard, and Urquard (121), while studying the reaction of bovine and human serum albumins with methyl orange, prepared dyes in which the SO_3^- group of methyl orange was replaced by the COO^-, PO_3H^-, or AsO_3H^- group. Sodium 3- and 4-(4-dimethylaminophenylazo)phenylphosphonates were prepared by coupling diazotized 3-aminophenylphosphonic or phosphanilic acids with *N*,*N*-dimethyl-*p*-phenylenediamine. The structure of the resulting azo compounds was not determined, and the authors state "analyses for carbon and hydrogen were considerably below theoretical, but it is probable that the impurity was merely sodium chloride."

Dickey (66) has patented a large number of dyes prepared by condensing 4-chloro-3-nitrophenylphosphonic acid with aniline or a substituted aniline to yield a 4-anilino-3-nitrophenylphosphonic acid. By using an ester or an amide rather than the phosphonic acid the corresponding phosphonic amides or esters were obtained. The resulting yellow dyes were of particular value in dyeing cellulose acetate textiles, but also dyed silk, wool, nylon, and other materials.

The dye and indicator properties of a limited series of phosphonic and arsonic acids containing azo groups have been recently reported (136). The compounds prepared were the phosphonic and arsonic acid analogs of methyl orange, ethyl orange, and Congo red. The various fabrics dyed with these dyes were subsequently laundered with commercial detergents; excellent fastness without running or fading was reported for each dye deposited on the particular fabric (cotton, silk, or wool) for which the dye showed an affinity. All of the arsonic acids and all but one of the phosphonic acids were indicators with two distinct color changes, as would be expected from the structure of these compounds. The phosphonic analog of ethyl orange, however, showed only a single color change from red to orange-red between pH 3.5 and 5.8.

E. REDUCTION OF PHOSPHONIC ACIDS

The difficulty in reducing phosphoric acid and its derivatives is well known; theoretical reasons for this have been discussed by Latimer (143). It is accordingly not surprising that the direct reduction of phosphonic acids has not been accomplished, although some evidence exists that benzylphosphonic acid may have been reduced to the corresponding phosphine with a large excess of phosphorous acid; the benzylphosphine itself was not characterized other than by its typical odor (149). Phosphorous acid in excess, as well as hypophosphorous acid, might possibly serve to reduce phosphonic acids to phosphines; this point should be investigated. An attempt to reduce phosphonic acids with a wide variety of other reducing agents proved unsuccessful (77). It was found, however, that phenylphosphonic dichloride, readily obtained by the reaction between phenylphosphonic acid and phosphorus pentachloride, could be easily reduced to phenylphosphine by the use of either lithium aluminum hydride or lithium borohydride. At about the same time, Karrer and Jucker (116) observed that when organic esters of phosphoric acid are treated with lithium aluminum hydride, the corresponding alcohol and a mixture of phosphoric acid and phosphine are obtained. In recent papers the reduction of phenyldichlorophosphine (94, 240) and phenylphosphinic acid (241) with lithium aluminum hydride to phenylphosphine has been reported. However, it has been stated that arylphosphonic acids cannot be reduced to the corresponding phosphines with lithium aluminum hydride (241).

By contrast with phenyldichlorophosphine bis(trifluoromethyl)iodophosphine was not reduced by lithium aluminum hydride but was readily reduced by hydrogen in the presence of Raney nickel (31, p. 3898).

The difficulty in reducing phosphonic acids allows the use of a wide variety of reducing agents for effecting the reduction of other groups in the molecule. Such reductions can be brought about either chemically or catalytically. It has recently been found possible to reduce arylphosphonic acids to the corresponding cyclohexylphosphonic acids by the use of hydrogen and a rhodium-on-alumina catalyst at low pressure (82). Although there is no reduction of the phosphono group, halogen substituents are cleaved from the ring.

F. PHOSPHONIC ACID CATION-EXCHANGE RESINS

The discovery of synthetic ion-exchange resins is one of the most important chemical discoveries of the past twenty years. Resins which contain sulfonic acid, carboxylic acid, or phenol groups are generally employed for the removal of cations from solution. It is not surprising that, with the increasing interest in phosphorus chemistry in recent years, phosphonic acid resins have been synthesized and tested. The first announcement of this type of resin was early in 1952

(41). Both phosphonic and phosphinic type resins were described in a preliminary communication. These resins were found to show a selectivity for sodium over potassium. Although the details of preparation of these materials have not been announced and a personal communication from the National Aluminate Corporation has indicated that they are no longer available, a later paper by Bregman reveals some of the properties of these interesting ion-exchange resins (40). As would be expected, titration of the phosphonic acid resin gives two breaks in the titration curve corresponding to the expected breaks for the phosphonic acid group. At low pH values the resin preferentially removes potassium rather than sodium, while at pH values above 6 sodium is removed preferentially over potassium. Carboxylic, phosphonic, and sulfonic acid type resins were compared; the reaction rate of these resins with cations is in the order $SO_3H > PO_3H_2 > COOH$.

A phosphonic acid type resin has been tested for its ability to remove sodium from the animal body (230). In contrast to the carboxylic and sulfonic acid type resins, the phosphonic acid resins had only a minimal effect in removing either potassium or sodium ions when administered to the extent of 10 per cent of the diet of rats. The resin used in this experiment was stated to be a "phosphonic type" of the structure $ROPO_3H_2$. If this formula is correct, the resin contains not phosphono but rather phosphoric ester groups.

The preparation of ion-exchange resins containing phosphonic acid groups is described in considerable detail in a recent paper (239). The resins were prepared by condensing various phenoxymethylphosphonic acids with formaldehyde. In alkaline solution a monomer of the type $HOCH_2C_6H_4OCH_2PO_3Na_2$ is first formed. When this salt is acidified in an excess of formaldehyde and heated at 140°C., an insoluble thermosetting resin, having ion-exchange properties, is formed. The same type of resin is obtained by heating a phenoxymethylphosphonic acid with an excess of formaldehyde. The resins are highly cross-linked in those cases where there are no substituents ortho or para to the phosphono group.

Several polystyrene phosphonic acids have been prepared as cation-exchange resins (2). The syntheses were accomplished by the reaction between either styrene or polystyrene, phosphorus trichloride, and aluminum chloride. The maximum cation-exchange capacity of the resulting resins was 250 millimoles of sodium per gram of resin, or 23 per cent of the theoretical capacity.

Another phosphonic acid cation-exchange resin is Duolite C-60, manufactured by the Chemical Process Company, Redwood, California; however, the only information obtainable on this resin is the statement that it is a phosphonic acid type resin (232).

G. CLEAVAGE OF THE CARBON–PHOSPHORUS BOND

Unsubstituted aromatic and aliphatic phosphonic acids are thermally stable compounds. This is in accord with the bond energy of the carbon–phosphorus bond which has been calculated as 62 kcal., compared with 57 kcal. for the carbon–arsenic bond, 68 kcal. for the carbon–silicon bond, and 64 kcal. for the carbon–carbon bond (95). Heating for long periods at relatively high temperatures does result in splitting of the carbon–phosphorus bond; 2-naphthylphosphonic acid, when heated in a sealed tube at 275°C. for 24 hr., gave naphthalene and metaphosphoric acid (144, 145). The carbon–phosphorus bond of phosphonic acids is resistant to chemical attack. Phenylphosphonic acid has been nitrated with nitric acid at 100°C. (171, p. 276), while it is common practice to recrystallize certain phosphonic acids from hot 6 *N* hydrochloric acid in order to ensure conversion of the sodium or potassium salts to the free acids (67). Octadecylphosphonic acid has been boiled for 8 hr. in sodium hydroxide solution or for 12 hr. in alcoholic potassium hydroxide and the free acid recovered in almost theoretical yield (50, p. 366).

Although the majority of substituted phosphonic acids are also quite stable, there are certain exceptions in both the aromatic and the aliphatic series. With aromatic phosphonic acids the presence of strongly electron-repelling groups in the ortho and para position to the phosphono group apparently weakens the carbon–phosphorus bond; such phosphonic acids are readily hydrolyzed to phosphoric acid and the substituted hydrocarbon under a variety of experimental conditions. *p*-Methoxyphenylphosphonic acid has been cleaved to anisole and phosphoric acid by 66 per cent hydrobromic acid in glacial acetic acid (146, 237) and by heating with 57 per cent hydriodic acid (24). *p*-Hydroxyphenylphosphonic acid, however, can be obtained in low yield, admixed with starting material, when *p*-methoxyphenylphosphonic acid is heated with 47 per cent hydrobromic acid (24). Similarly the carbon–phosphorus bond in 2-methoxy-4-nitrophenylphosphonic acid was cleaved when this acid was refluxed in 48 per cent hydrobromic acid, whereas the ether linkage only was cleaved in 40 per cent hydrobromic acid (70). 2-Methoxy-4-nitrophenylphosphonic acid was readily reduced to the corresponding amino compound by Raney nickel and hydrogen in alkaline solution, but 2-hydroxy-4-nitrophenylphosphonic acid was converted to *m*-aminophenol and phosphoric acid under the same conditions; the latter phosphonic acid was successfully reduced with platinum and hydrogen in dilute hydrochloric acid solution (70). The hydrolysis of *p*-methoxyphenylphosphonic acid to anisole and phosphoric acid in sulfuric acid solution has been studied kinetically (238). The reaction was found to be first order in phosphonic acid but was more complex in H^+. Thus, in sulfuric acid of concentrations from 9 to 30 per cent, the reaction rate increased as the square of the acid concentration, but above 30 per cent the rate of increase became slower and was even more markedly slowed as the concentration approached 60 per cent.

The instability of *p*-dimethylaminophenylphosphonic acid in aqueous solution was noted by Schenk and Michaelis many years ago (220). These same authors also noted that the corresponding phosphinic acid, *p*-$(CH_3)_2NC_6H_4PO_2H_2 \cdot 2H_2O$, was hydrolyzed to phosphorous acid and dimethylaniline by warming in aqueous solution. The hydrolysis was faster in acid solution, but the compound was stable in alcoholic or in alkaline solution. In contrast to these findings, the cleavage of the carbon–phosphorus bond in a number of alkylaminophenylphosphonic acids in alkaline solution has been described (69). The phenomenon was noted in an attempt to prepare *o*- and *p*-alkylaminophenylphosphonic acids by the reaction between the corresponding bromo acids and various alkylamines in aqueous solution in the presence of cuprous oxide. *p*-Methylaminophenylphosphonic acid and a few others were successfully prepared. In the majority of cases, however, no alkylaminophenylphosphonic acid could be isolated, although bromide-ion analyses indicated that all the bromine had been split from the ring. Analysis of reaction mixtures indicated that usually from 10 to 25 per cent of the phosphorus was present as phosphoric acid; failure to isolate the desired phosphonic acid was attributed to the solubility of these compounds in aqueous phosphoric acid. No difficulty was experienced in preparing *m*-alkylamino compounds, and analyses of the reaction mixtures indicated that essentially no phosphoric acid was present.

Aminophenylphosphonic acids are apparently more stable than the alkylamino compounds discussed above. However, the carbon–phosphorus bond in these compounds can be broken under some circumstances. *o*-Aminophenylphosphonic acid (and presumably also the para isomer) gives a quantitative yield of tribromoaniline when treated with bromine water (68, 125), whereas the meta compound is brominated without rupture of the carbon–phosphorus bond (179, p. 468). Bell and Kosolapoff (24) have stated that *p*-aminophenylphosphonic acid shows a "low order of stability of the carbon-to-phosphorus link," but no experimental evidence is given. *p*-Aminophenylphosphinic acid is unstable and is cleaved to aniline and phosphorous acid by prolonged boiling in acid solution (146). *p*-Hydroxyphenylphosphonic acid also is unstable in aqueous acid solution; it gives tribromophenol when treated with bromine water (24).

In contrast to the situation in arylphosphonic acids, in which the carbon–phosphorus bond is weakened by electron-releasing substituents, the carbon–phosphorus bond in alkylphosphonic acids appears to be weakened by certain electron-attracting groups in close proximity to the phosphono group. In particular, compounds in which a carbonyl group is attached directly to the phosphono group are rather unstable (50). Thus, dialkyl acylphosphonates cannot be hydrolyzed to the corresponding acids without cleavage of the carbon–phosphorus bond; acetyl- and benzoylphosphonic acids have, however, been prepared from the esters by the use of anhydrous hydrogen bromide (58). When the carbonyl group is in the α-position, the carbon–phosphorus bond is probably more stable but may be cleaved by acid hydrolysis (50). The possibility of rupture of the carbon–phosphorus bond in α-carbonylphosphonic esters has been used to help in establishing the structure of several compounds. Diethyl phosphonate adds to α,β-unsaturated ketones to give saturated oxophosphonic diesters. Hydrolysis of these esters gives the free phosphonic acids and not phosphoric acid. From these results it has been concluded that the diethylphosphono group added β to the carbonyl group (203, 204).

In addition to the carbonyl group a few other groups have been found to affect the stability of the carbon–phosphorus bond in aliphatic phosphonic acids. Diethyl α-methyl-β-styrylphosphonate is cleaved to α-methylstyrene and phosphoric acid when heated with hydrochloric acid (8). It was originally claimed that when dialkyl trichloromethylphosphonates were hydrolyzed with 15 per cent hydrochloric acid the carbon–phosphorus bond was cleaved to give the alkyl chloride, carbon dioxide, and phosphorous acid (114). More recent work on this subject, however, has disproved this claim, and it has now been shown that trichloromethylphosphonic acid can be readily obtained by the hydrolysis of its esters by hydrochloric acid (29, 63, 248, 250, 252). In contrast to the stability of trichloromethylphosphonic acid to acid hydrolysis, the carbon–phosphorus bond in esters of this compound is readily cleaved when warmed in alkaline solution (27, 248, 251).

It is of interest to note that trifluoromethylphosphonic acid is an extremely stable compound, whereas other phosphorus compounds containing the trifluoromethyl group, e.g., CF_3PH_2, $(CF_3)_2PH$, $(CF_3)_2POH$, are decomposed in alkaline solution with rupture of the carbon–phosphorus bond (31).

An interesting difference exists between α-hydroxyphosphonic acids and their esters. The acids have long been known and are extremely stable substances. After being boiled in concentrated alkali solutions 1-hydroxyisopentylphosphonic acid was recovered unchanged, and even repeated evaporations with nitric acid or aqua regia failed to completely break the carbon–phosphorus bond (74). The carbon–phosphorus bond in the esters is also quite stable towards acids, and the corresponding phosphonic acids can be readily obtained from the esters by acid hydrolysis. By contrast with the acids, however, the esters are rapidly cleaved by alkali to give the aldehyde and the dialkyl phosphonate (1, 56, 176):

$$RCHOHPO(OR')_2 \rightleftharpoons RCHO + HPO(OR')_2$$

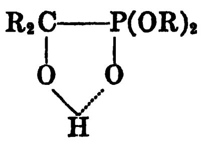
Some of the esters are similarly cleaved merely by warming (1). It should be noted that this reaction, unlike those previously described, is not a hydrolysis. Thus, a dialkyl phosphonate and a carbonyl compound are formed rather than a dialkyl phosphate and an alcohol.

The reason for the difference in stability between the α-hydroxyphosphonic acids and their esters has been the subject of considerable discussion (176). A mechanism for the alkaline-catalyzed cleavage of the esters has been proposed (1). This involves the following steps: (*a*) addition of a sodium ion to the oxygen of the PO group, (*b*) an electron flow from the carbon–phosphorus linkage facilitated by an electron shift from the hydroxyl group, and (*c*) rupture of the carbon–phosphorus bond. This mechanism seems highly improbable.

In order to account for the thermal dissociation of these esters, these same authors suggest an equilibrium between the dialkyl α-hydroxyphosphonate and the aldehyde (or ketone) plus dialkyl phosphonate:

$$R_2COHPO(OR)_2 \rightleftharpoons R_2CO + HPO(OR)_2$$

They further suggest that an intramolecular hydrogen bond exists in the ester (IV), which facilitates transfer of the hydrogen from the carbonyl group to the oxygen of the P—O group.

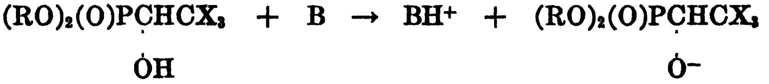


IV

The hydrolytic cleavage of the α-hydroxyphosphonic esters in alkaline solution takes an entirely different course in the case of dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonate. With this compound, hydrogen chloride is eliminated, the phosphorus–carbon bond is ruptured, and the compound rearranges to a phosphate ester (19, 151, 157).

$$CCl_3CHOHPO(OR)_2 \xrightarrow{OH^-} Cl_2C{=}CHOPO(OR)_2 + HCl$$

Bengelsdorf (28) has advanced evidence to show that this type of reaction is quite general for certain types of α-hydroxyphosphonic diesters. The first step in the reaction is probably the removal of a proton from the α-hydroxy group:

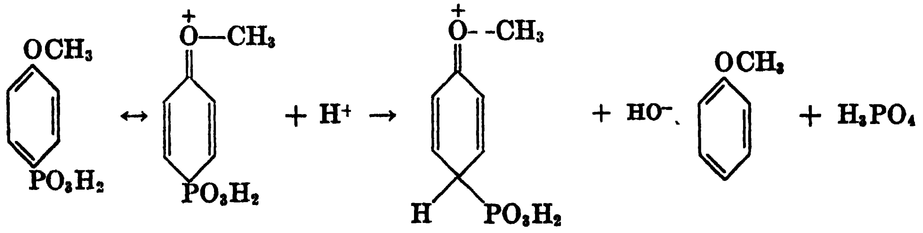


$$(RO)_2(O)P\underset{OH}{C}HCX_3 + B \rightarrow BH^+ + (RO)_2(O)P\underset{O^-}{C}HCX_3$$

If X is a group which is capable of leaving as an anion, then rearrangement to a vinyl phosphate will occur as the next step. Alternatively, where the ionization of X is energetically unfavorable, the ester will be cleaved to the dialkyl phosphonate and the aldehyde.

Although these suggestions by Abramov and by Bengelsdorf may be correct, they do not offer any explanation for the thermal instability of these esters, nor any reason why the acids are so much more stable than the esters in alkaline solution. The diethylphosphono group has been shown, at least in reactions of aromatic compounds, to be strongly electron-attracting, with Hammett σ-constants of 0.55 and 0.66 for the meta and para positions, respectively (83). By contrast, the PO_3^{--} group is electron-repelling in both aliphatic (223) and aromatic (101) compounds, with σ-constants of −0.02 and −0.16 in the meta and para positions. This marked difference in the electrical effects of the two groups may well be a contributing factor to the difference in stability between the two classes of compounds.

There has been very little theoretical investigation as to the reasons for the instability of the carbon–phosphorus bond in some substituted aryl and alkyl phosphonic acids. Lesfauries (146) has proposed the following mechanism for the hydrolytic cleavage of aromatic phosphonic acids substituted with electron-repelling groups:



The cleavage of the phosphorus as a positively charged phosphonyl group, $PO_3H_2^+$, is facilitated by electron-repelling groups. Presumably then the $PO_3H_2^+$ group would react with the solvent to give phosphoric acid and a proton. The proposed mechanism also is believed to account for the decreased stability of the arylphosphinic acids as compared with the phosphonic acids, since the phosphorus is more positive in the former compounds. In amino-substituted phosphonic acids, however, the substituent is present largely as a positively charged ammonio group. The instability of aminophosphonic acids in acid solution must then be due to the small proportion of the compound which contains an uncharged amino group.

Any mechanism for the instability of the carbon–phosphorus bond in some phosphonic acids must account for the fact that electron-repelling substituents apparently weaken the bond in aromatic compounds, while electron-attracting substituents weaken the bond in aliphatic compounds. Obviously the question of the stability of the carbon–phosphorus bond in substituted phosphonic acids requires further investigation.

IV. PHYSICAL PROPERTIES AND STRUCTURE OF PHOSPHONIC ACIDS

A. ABSORPTION SPECTRA

The ultraviolet absorption spectra of a considerable number of arylphosphonic acids have been determined in 95 per cent ethanol (76, 80, 99, 100). The spectra of some of these compounds have been measured in water also (189). In general the phosphono group causes no profound change in the characteristics of the spectrum of the parent compound. The absorption maxima of most arylphosphonic acids show bathochromic shifts of about 10 mμ, and the intensity of absorption is increased by a factor between 1.5 and 5. Any fine structure found in the spectrum of the parent compound is usually unaltered by the presence of the phosphono group. It seems likely that the slight bathochromic shift and the moderate hyperchromic effect should be ascribed to *weak* resonance interaction between this group and the benzene ring.

Two cases have been recorded in which the phosphono group *does* have a marked effect on the spectrum of the parent compound. The ultraviolet absorption of *o*-nitrophenylphosphonic acid is much less intense than that of nitrobenzene. This effect has been attributed to steric interference with the resonance between the nitro group and the benzene ring (80). Similarly, a PO_3H_2 group in the ortho position of biphenyl greatly reduces the intensity of the biphenyl absorption (76). Presumably, therefore, the *o*-phosphono group interferes with the attainment of a planar arrangement of the two phenyl rings, and thus hinders resonance interaction between them.

The ultraviolet absorption spectra of the species $C_6H_5PO_3H_2$, $C_6H_5PO_3H^-$, and $C_6H_5PO_3^{--}$ in perchlorate solutions of ionic strength 1.0 have also been determined (17, p. 429).

No systematic study of the infrared spectra of phosphonic acids has been published. The scanty information available on this subject has been recently reviewed (25).

B. MOLECULAR WEIGHTS

It is well known that organic compounds which contain groups such as —OH, $—NH_2$, —COOH, =NOH, and =NH are generally polymeric in nonpolar solvents and that the apparent molecular weight increases as the concentration increases. This phenomenon has been explained by intermolecular hydrogen bonding (142). It is therefore not surprising to find that phosphonic acids are associated in nonpolar solvents. Both *n*-butyl- and *n*-hexylphosphonic acids have been found to be associated in naphthalene solution and their molecular weights increase with increasing concentration (134). Similarly, *o*- and *m*-tolylphosphonic acids were associated in naphthalene solution, and *o*- and *p*-tolylphosphonic acids were associated both in acetone and in camphor (16).

In accordance with the well-known properties of compounds associated by hydrogen bonding, both aliphatic and aromatic phosphonic acids have been found to be monomolecular in acetic acid (81). In water the molecular-weight determinations were complicated by ionization of the strong phosphonic acid group, but in all cases the apparent molecular weight was less than the formula weight (16).

In two other papers two phosphonic acids, tetralinphosphonic acid (2) and trimethylsilylmethylphosphonic acid (118), have been reported as monomolecular, but in neither case was the solvent given. (A personal communication from Dr. W. H. Keeber indicates that the molecular weight of the latter compound was determined only by potentiometric titration and is thus a neutral equivalent rather than a true molecular weight.)

Kosolapoff has proposed that phosphonic acids are associated in long chains through intermolecular hydrogen bonding and that this association persists in aqueous solution (129), so that the neutralization of a phosphonic acid solution by aqueous alkali consists of a neutralization of the free chain ends with preservation, in whole or in part, of the essential structure of the chain, until one formula weight is one-quarter neutralized, whereupon the dimeric hemi-alkali salt is formed. Kosolapoff neutralized a solution of *n*-butylphosphonic acid with small increments of alkali and evaporated the solutions to dryness after each step. The wax-like solids which were obtained up to one-quarter neutralization melted below the melting point of the free acid. Kosolapoff has interpreted these results as being consistent with the foregoing association concept.

As suggested previously in this review, the hydrogen-bonded dimeric form for the hemi-alkali salts may well be correct. However, the energy of the hydrogen bond is so weak—on the order of 5 kcal.—that compounds associated by hydrogen bonds are rapidly dissociated when dissolved in polar solvents such as water, acetic acid, or formic acid. It is true that benzoic acid is partially dimeric in aqueous solution (117) and it has been proposed that in certain favorable cases intramolecular hydrogen bonds are maintained with some acids in aqueous solutions (159). However, in these cases steric considerations greatly favor the hydrogen bonding, and even with benzoic acid the polymerization does not exceed the dimeric form. The molecular weights of phosphonic acids in acetic acid show these compounds to be monomeric in that solvent. The low melting points and wax-like character of partially neutralized *n*-butylphosphonic acid seem insufficient evidence for assigning a polymeric structure to phosphonic acids in aqueous solution, especially since many phosphonic acids can be readily crystallized from aqueous solution. More experimental data are needed to settle this question.

C. THE CHARACTER OF THE PHOSPHORUS–OXYGEN BOND

The nature of the phosphorus–oxygen bond in the phosphoryl (≡PO) group has long been a subject of controversy. Before the Lewis theory of electronic structure, compounds such as phosphonic acids were believed to contain pentavalent phosphorus and the oxygen of the phosphoryl group was thought to be linked to the phosphorus by a double bond. The octet theory of Lewis required that the phosphorus–oxygen bond be semipolar, and this view has been widely accepted. However, there is considerable evidence that the phosphorus atom can expand its valence shell to ten electrons and be involved in multiple-bond formation. For example, it has been shown that the wavelength of the phosphoryl stretching vibration in a variety of organic phosphorus compounds varies (from 7.0 to 8.5 μ) with the electron-repelling power of the groups linked to the phosphorus atom (23). Such a change in wavelength implies a change in the force constant of the bond and a corresponding change in the bond order. In compounds containing strongly electron-repelling substituents, the phosphoryl bond probably approaches the nature of a pure single bond. On the other hand, when the substituents are strongly electron-attracting, the phosphoryl group may take on appreciable multiple-bond character. Cyclohexylphosphonic acid is the only phosphonic acid for which infrared data have been published (26). The wavelength of the phosphoryl absorption in this compound is 8.2 μ, which is near the highest values observed for the ≡PO bond. Accordingly, the infrared evidence suggests that the phosphoryl bond of the phosphono group is primarily a single covalent bond.

Chemical studies have also provided evidence that the phosphorus atom can expand its valence shell. As has been mentioned in the section on nitration, the principal by-product of the nitration of phenylphosphonic acid is *o*-nitrophenylphosphonic acid. This fact indicates that the phosphono group is conjugated with the ring, since purely inductive meta-directing substituents favor the formation of the para isomer as a by-product, while the ortho isomer is favored only when resonance is possible between the meta-directing substituent and the ring (96). Therefore, the phosphorus atom in the phosphono group must have π-orbitals which can interact with the π-electrons of the benzene ring.

It has been reported that tetraethyl methylenediphosphonate reacts readily with potassium and that the resulting potassium derivative can be alkylated with *n*-butyl bromide (131). The enhanced reactivity of the hydrogen in the methylene group of the diphosphonate has been cited as evidence for a "keto-enol" type of tautomerism in the compound:

$$(C_2H_5O)_2(O)PCH_2P(O)(OC_2H_5)_2 \rightleftharpoons (C_2H_5O)_2(O)PCH{=}P(OH)(OC_2H_5)_2$$

Obviously, such an equilibrium can exist only if the phosphorus atom can expand its valence shell to at least ten electrons.

Studies of compounds that do not contain the phosphoryl group have also produced evidence that the phosphorus can expand its valence shell. Thus, the preparation of pentaphenylphosphorus shows that stable, truly pentavalent organophosphorus compounds can exist (215, 247). Evidence for phosphorus-to-phosphorus double bonds is provided by the fact that phosphorobenzene ($C_6H_5P{=}PC_6H_5$) is unassociated in camphor solution (240).[1]

V. Biological Properties of Phosphonic Acids

In contrast to the organic arsenicals, no systematic investigation into the possible therapeutic properties of organic phosphorus compounds has ever been undertaken. Earlier workers tested phosphanilic (*p*-aminophenylphosphonic) acid and a number of related compounds against a few microörganisms, usually *in vitro*. Several were found to show antibacterial activity (21, 115, 122, 138, 228). A preliminary investigation also revealed that phosphanilic acid is very nontoxic to laboratory animals (186). A more thorough investigation of a larger series of aromatic phosphonic and phosphinic acids against fifteen different microörganisms *in vitro* has revealed that many of these compounds possess antibacterial activity (233). Phosphanilic acid was the most active compound tested; it was superior to sulfanilamide against many organisms, although inferior to sulfathiazole. None of the compounds tested possessed any fungicidal activity. One phosphinic acid possessed some activity against *Treponema pallidum*, the causative agent of syphilis. In testing a large series of compounds against *Borrelia novyi*, the causative agent of relapsing fever, *p*-aminobenzylphosphonic acid was found to be without activity (234).

A number of aminoalkylphosphonic acids have been found to be toxic in high concentration to silk worms and chick embryos (219). These same compounds also repressed tobacco mosaic virus and tobacco rootlets. The compounds did not act as competitors of amino acids. Kidney, liver, and plant tissue did not split the carbon–phosphorus bond in the phosphonic acids tested.

In an investigation into the effect of various substances on the uptake of methionine by *Escherichia coli*, it was found that aminomethylphosphonic acid was a weak inhibitor of methionine uptake, although aminomethanesulfonic and α-aminoethanesulfonic acids stimulated the methionine uptake (165).

Phosphonic acids are active as inhibitors of certain enzymes. Thus, in testing a fairly large series of aromatic phosphonic and phosphinic acids and their esters against cholinesterase, it was found that many of these compounds possessed anticholinesterase activity (84, 231). The most active phosphonic acid was the *o*-iodo derivative. None of the organic phosphorus compounds tested approached

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[1] Note added in proof: A recent note by W. Kuchen and H. Buchwald (Angew. Chem. 68, 791 (1956)) suggests that phosphorobenzene may be decomposed in molten camphor and hence may not be monomolecular in that solvent. H. Mahler and A. B. Burg (J. Am. Chem. Soc. 79, 251 (1957)) have recently proposed that phosphorobenzene actually has a ring structure.

TABLE 7

Aliphatic and alicyclic phosphonic acids

Phosphonic Acid	Formula	Melting Point	References
	C_1 acids		
		°C.	
Bromomethyl-	$BrCH_2PO_3H_2$	62	(63)
Chloromethyl-	$ClCH_2PO_3H_2$	89–90	(63, 111, 112, 113, 120, 190, 249, 252)
Dichloromethyl-	$Cl_2CHPO_3H_2$	116–119	(63, 248)
Iodomethyl-	$ICH_2PO_3H_2$	89	(63)
Trichloromethyl-	$Cl_3CPO_3H_2$	163.5	(29, 63, 119, 240, 250, 252)
Trifluoromethyl-	$F_3CPO_3H_2$	81–82	(30)
	C_2 acids		
Acetyl-	$CH_3COPO_3H_2$	108–114	(58)
1-Aminoethyl-	$CH_3CH(NH_2)PO_3H_2$	>340	(47)
1-Chloroethyl-	$CH_3CHClPO_3H_2$	99–100	(111, 249)
2-Hydroxyethyl-	$HOCH_2CH_2PO_3H_2$	—	(190)
	C_3 acids		
1-Amino-1-methylethyl-	$(CH_3)_2C(NH_2)PO_3H_2 \cdot H_2O$	258	(109, 160, 161)
1-Aminopropyl-	$C_2H_5CH(NH_2)PO_3H_2$	>350	(47)
3-Chloropropyl-	$ClCH_2CH_2CH_2PO_3H_2$	95–97.5	(229)
2,3-Dihydroxypropyl-	$HOCH_2CHOHCH_2PO_3H_2$		(10, 191)
2-Hydroxypropyl-	$CH_3CHOHCH_2PO_3H_2$		(191)
3-Hydroxypropyl-	$HOCH_2CH_2CH_2PO_3H_2$		(229)
β-Phosphonoalanine-	$HOOCCH(NH_2)CH_2PO_3H_2$		(51)
Propylenedi-	$CH_3CH(PO_3H_2)CH_2PO_3H_2$	123	(191, 222)
	C_4 acids		
1-Amino-1-methylpropyl-	$C_2H_5(CH_3)C(NH_2)PO_3H_2 \cdot H_2O$	262	(160, 161)
sec-Butyl-	$C_2H_5CH(CH_3)PO_3H_2$	54–56	(62)
tert-Butyl-	$(CH_3)_3CPO_3H_2$	191.5–192	(62)
1-Chlorobutyl-	$C_3H_7CHClPO_3H_2$	86–87	(111)
1-Hydroxybutyl-	$C_3H_7CHOHPO_3H_2$	154.5–155.0	(176)
1-Methylamino-1-methylethyl-	$CH_3NHC(CH_3)_2PO_3H_2$	140	(163)
3-Oxobutyl-	$CH_3COCH_2CH_2PO_3H_2$	81–82	(177)
3-Phosphonobutyric acid	$HOOCCH_2CH(CH_3)PO_3H_2$	141–143	(35, 36, 197, 200)
Tetramethylenedi-	$(CH_2)_4(PO_3H_2)_2$	—	(223)
Trimethylammoniomethyl-	$(CH_3)_3\overset{+}{N}CH_2PO_3H^-$	267	(108)
Trimethylsilylmethyl-	$(CH_3)_3SiCH_2PO_3H_2$	119–121	(118)
	C_5 acids		
1-Acetamido-1-methylethyl-	$CH_3CONHC(CH_3)_2PO_3H_2$	199–200	(162)
1-Amino-1-methylbutyl-	$C_3H_7C(CH_3)(NH_2)PO_3H_2 \cdot H_2O$	262–263 (d.)	(161)
1-Dimethylamino-1-methylethyl-	$(CH_3)_2NC(CH_3)_2PO_3H_2$	220–223	(163)
1,1-Dimethylpropyl-	$C_2H_5C(CH_3)_2PO_3H_2$	139–141	(62)
Furfuryl-	$C_5H_5OPO_3H_2$	—	(10)
Hydroxy-[4-(2,6-dihydroxy)pyrimidyl]-methyl-	$2,6\text{-}(HO)_2C_4HN_2CHOHPO_3H_2$	204–205.5 (d.)	(45)
Hydroxy-[4-(6-hydroxy)pyrimidyl]-methyl-	$6\text{-}HOC_4H_2N_2CHOHPO_3H_2$	226 (d.)	(45)
2-Methyl-4-thiazolylmethyl-, hydrochloride	$C_4H_4NSCH_2PO_3H_2 \cdot HCl$	142	(9)
4-Oxopentyl-	$CH_3CO(CH_2)_3PO_3H_2$	—	(12)
Pentylidenedi-	$CH_3(CH_2)_3CH(PO_3H_2)_2$	163–165	(131)
(Phosphonomethylimino)diacetic acid	$(HOOCCH_2)_2NCH_2PO_3H_2$	—	(221)
Tetrahydrofurfuryl-	$C_5H_9OPO_3H_2$	—	(10)

TABLE 7—*Continued*

Phosphonic Acid	Formula	Melting Point	References
C_6 acids			
		°C.	
1-Aminocyclohexyl-	$C_6H_{10}(NH_2)PO_3H_2 \cdot H_2O$	238	(160, 161)
4-Aminocyclohexyl-	$4\text{-}NH_2C_6H_{10}PO_3H_2$	>300	(82)
1-Cyclohexen-1-yl-	$C_6H_9PO_3H_2$	132–133	(72)
2-Cyclohexen-1-yl-	$C_6H_9PO_3H_2$	104–106	(72)
1,2-Dibromocyclohexyl-	$C_6H_9Br_2PO_3H_2$	162–163	(72)
2,3-Dibromocyclohexyl-	$C_6H_9Br_2PO_3H_2$	195–195.5	(72)
1,1-Dimethyl-3-oxobutyl-	$CH_3COCH_2C(CH_3)_2PO_3H_2$	—	(198)
1,2-Dimethyl-3-oxobutyl-	$CH_3COCH(CH_3)CH(CH_3)PO_3H_2$	—	(198)
Ethylenebis(nitrilodimethylene)tetra-	$[CH_2N(CH_2PO_3H_2)_2]_2$	—	(33, 245)
2-Ethyl-4-thiazolylmethyl-, hydrochloride	$C_5H_7NSCH_2PO_3H_2 \cdot HCl$	130–135	(9)
1-Hydroxycyclohexyl-	$1\text{-}HOC_6H_{10}PO_3H_2$	191–192	(72)
Hydroxy(4-pyridyl)methyl-	$4\text{-}C_5H_4NCHOHPO_3H_2 \cdot H_2O$	226–227 (d.)	(45)
5-Methoxy-2-pentenyl-	$CH_3OCH_2CH_2CH{=}CHCH_2PO_3H_2$	—	(202)
2-(4-Methyl-5-thiazolyl)ethyl-, hydrochloride	$C_6H_8NSPO_3H_2 \cdot HCl$	155–156	(45)
1-Methyl-1-(trimethylammonio)ethyl-	$(CH_3)_3\overset{+}{N}C(CH_3)_2PO_3H^- \cdot H_2O$	230–231 (d.)	(163)
2-Phosphonohexanoic acid	$CH_3(CH_2)_3CH(COOH)PO_3H_2$	170–172	(135)
(2-Phosphonoethylimino)diacetic acid	$(HOOCCH_2)_2NCH_2CH_2PO_3H_2$	—	(221)
C_7 acids			
α-Amino-*o*-hydroxybenzyl-	*o*-$HOC_6H_4CH(NH_2)PO_3H_2$	—	(47)
α-Amino-*p*-hydroxybenzyl-	*p*-$HOC_6H_4CH(NH_2)PO_3H_2$	150–152	(47)
1-Amino-1-propylbutyl-	$(C_3H_7)_2C(NH_2)PO_3H_2$	192	(161)
Benzoyl-	$C_6H_5COPO_3H_2$	—	(58)
o-Bromobenzyl-	*o*-$BrC_6H_4CH_2PO_3H_2$	182–183	(152)
p-Bromophenoxymethyl-	*p*-$BrC_6H_4OCH_2PO_3H_2$	166–168	(239)
α-Chlorobenzyl-	$C_6H_5CHClPO_3H_2$	98–99	(111)
α-Chloro-*p*-chlorobenzyl-	*p*-$ClC_6H_4CHClPO_3H_2$	152–153	(111)
o-Chlorophenoxymethyl-	*o*-$ClC_6H_4OCH_2PO_3H_2$	133–134	(153)
p-Chlorophenoxymethyl-	*p*-$ClC_6H_4OCH_2PO_3H_2$	156–157	(153, 239)
2,4-Dichlorophenoxymethyl-	$2,4\text{-}Cl_2C_6H_3OCH_2PO_3H_2$	141–143	(153, 239)
2,5-Dimethyl-3-oxocyclopentyl-	$2,5\text{-}(CH_3)_2\text{-}3\text{-}OC_5H_5PO_3H_2$	—	(106)
2-Hydroxy-5-nitrobenzyl-	$2\text{-}HO\text{-}5\text{-}NO_2C_6H_3CH_2PO_3H_2$	224–229	(152)
4-Hydroxy-3-nitrobenzyl-	$4\text{-}HO\text{-}3\text{-}NO_2C_6H_3CH_2PO_3H_2$	238	(152)
4-Methylcyclohexyl-	$CH_3C_6H_{10}PO_3H_2$	107–110	(82)
1-Methyl-3-oxocyclohexyl-	$1\text{-}CH_3\text{-}3\text{-}OC_6H_8PO_3H_2$	—	(106)
5-Methyl-3-oxo-4-hexenyl-	$(CH_3)_2C{=}CHCOCH_2CH_2PO_3H_2$	—	(204)
Nicotinamidomethyl-	$C_5H_4NCONHCH_2PO_3H_2 \cdot H_2O$	232–233 (d.)	(53)
Phenoxymethyl-	$C_6H_5OCH_2PO_3H_2$	141–142	(153, 239)
2,4,5-Trichlorophenoxymethyl-	$2,4,5\text{-}Cl_3C_6H_2OCH_2PO_3H_2$	179–180	(153, 239)
2,4,6-Trichlorophenoxymethyl-	$2,4,6\text{-}Cl_3C_6H_2OCH_2PO_3H_2$	217–218	(153)
C_8 acids			
α-Amino-*p*-methoxybenzyl-	*p*-$CH_3OC_6H_4CH(NH_2)PO_3H_2$	215–218	(47)
α-Amino-(3-methoxy-4-hydroxy)-benzyl-	$3\text{-}CH_3O\text{-}4\text{-}HOC_6H_3CH(NH_2)PO_3H_2$	215	(107)
α-Amino-*α*-methybenzyl-	$C_6H_5C(CH_3)(NH_2)PO_3H_2 \cdot H_2O$	235	(161)
α-Amino-*p*-methylbenzyl-	*p*-$CH_3C_6H_4CH(NH_2)PO_3H_2$	276	(107)
1-Amino-2-phenylethyl-	$C_6H_5CH_2CH(NH_2)PO_3H_2$	225-227	(47)
α-Aminopiperonyl-	$3,4\text{-}CH_2O_2C_6H_3CH(NH_2)PO_3H_2$	255	(105, 107)
Benzamidomethyl-	$C_6H_5CONHCH_2PO_3H_2$	185–186 (d.)	(104)
α-Chloro-*p*-methylbenzyl-	*p*-$CH_3C_6H_4CHClPO_3H_2$	150–151	(111)
2-Chlorostyryl-	$C_6H_5CCl{=}CHPO_3H_2$	159–160	(253)
2-Ethylcyclohexyl-	$2\text{-}C_2H_5C_6H_{10}PO_3H_2$	135–138	(82)
4-Ethylcyclohexyl-	$4\text{-}C_2H_5C_6H_{10}PO_3H_2$	103–106	(82)
N,*N'*-Ethylenebis(*N*-phosphonomethylglycine)	$[(HOOCCH_2)(CH_2PO_3H_2)NCH_2]_2$	—	(34)

TABLE 7—*Continued*

Phosphonic Acid	Formula	Melting Point	References
C_8 acids—*continued*			
		°C.	
α-Methylbenzyl-	$C_6H_5CH(CH_3)PO_3H_2$	—	(58)
(*N*-Methylnicotinamido)methyl-	$C_5H_4NCON(CH_3)CH_2PO_3H_2$	180–181	(53)
2-Oxo-2-phenylethyl-	$C_6H_5COCH_2PO_3H_2$	143	(201)
Phenylethylenedi-	$C_6H_5CH(PO_3H_2)CH_2(PO_3H_2)$	212–214	(8)
o-Tolyloxymethyl-	*o*-$CH_3C_6H_4OCH_2PO_3H_2$	157–158	(239)
m-Tolyloxymethyl-	*m*-$CH_3C_6H_4OCH_2PO_3H_2$	115–117	(239)
C_9 acids			
α-Acetamidobenzyl-	$C_6H_5CH(NHCOCH_3)PO_3H_2$	188	(162)
α-Dimethylaminobenzyl-	$C_6H_5CH[N(CH_3)_2]PO_3H_2$	230 (d.)	(163)
2,4-Dimethylbenzyl-	2,4-$(CH_3)_2C_6H_3CH_2PO_3H_2$	184–186	(152)
α,β-Diphosphonodihydrocinnamic acid	$C_6H_5CH(PO_3H_2)CH(PO_3H_2)COOH$	113–115	(213)
(*N*-Ethylnicotinamido)methyl-	$C_5H_4NCON(C_2H_5)CH_2PO_3H_2$	185–186	(53)
1-Hydroxy-3-phenylpropyl-	$C_6H_5CH_2CH_2CHOHPO_3H_2$	174.5–175	(176)
3-Oxo-3-phenylpropyl-	$C_6H_5COCH_2CH_2PO_3H_2$	123–124	(177)
α-Phosphonocinnamic acid	$C_6H_5CH{=}C(COOH)PO_3H_2$	132	(210)
4-Phosphono-3,4-dihydrocoumarin	$\underline{C_6H_4OCOCH_2C}HPO_3H_2$	218–220	(14)
β-Phosphonodihydrocinnamic acid	$C_6H_5CH(PO_3H_2)CH_2COOH$	204	(35, 36, 197)
Phthalimidomethyl-	*o*-$C_6H_4(CO)_2NCH_2PO_3H_2$	280–285	(108)
C_{10} acids			
α-Amino-*p*-isopropylbenzyl-	*p*-$(CH_3)_2CHC_6H_4CH(NH_2)PO_3H_2$	267 (d.)	(107)
1-Benzamido-1-methylethyl-	$C_6H_5CONHC(CH_3)_2PO_3H_2$	197	(162)
α-Butyl-α-phosphonocaproic acid	$(n\text{-}C_4H_9)_2C(COOH)PO_3H_2$	140–141	(135)
$α^1,α^4$-Durenedi-	2,5-$(CH_3)_2C_6H_2$-1,4-$(CH_2PO_3H_2)_2$	340–350	(152)
$α^1,α^5$-Durenedi-	2,4-$(CH_3)_2C_6H_2$-1,5-$(CH_2PO_3H_2)_2$	—	(152)
Hydroxy(3-isoquinolyl)methyl-	$C_9H_6NCHOHPO_3H_2$	238–239 (d.)	(45)
4-Methyl-4-phosphono-3,4-dihydrocoumarin	$C_6H_4OCOCH_2C(CH_3)PO_3H_2$	192–193	(14)
2-Phenyl-4-thiazolylmethyl-, hydrochloride	$C_6H_5C_3HNSCH_2PO_3H_2 \cdot HCl$	180–181	(9)
2,3-Quinoxalinebis(methyl-)	$C_8H_4N_2(CH_2PO_3H_2)_2$	234 (d.)	(13)
2-(1,2,3,4-Tetrahydronaphthyl)-*	$C_{10}H_{11}PO_3H_2$	209	(148)
C_{11} acids			
p-*tert*-Butylphenoxymethyl-	*p*-$(CH_3)_3CC_6H_4OCH_2PO_3H_2$	132–134	(239)
Carvacrylmethyl-	2-CH_3-5-$(CH_3)_2CHC_6H_3CH_2PO_3H_2$	175–177	(152)
10-Chloro-11-phosphonohendecanoic acid	$HOOC(CH_2)_8CHClCH_2PO_3H_2$	116–117	(50)
Hydroxy-1-naphthylmethyl-	$C_{10}H_7CHOHPO_3H_2$	156–158	(60)
2-(*p*-Methoxyphenyl)-4-thiazolylmethyl-, hydrochloride	*p*-$CH_3OC_6H_4C_3HNSCH_2PO_3H_2 \cdot HCl$	184–186	(9)
1-Naphthylmethyl-	$C_{10}H_7CH_2PO_3H_2$	212	(60)
2-Naphthylmethyl-	$C_{10}H_7CH_2PO_3H_2$	229–230	(7)
C_{12} acids			
1-Acenaphthenol-1-	$C_{12}H_9OPO_3H_2$	195	(61)
1-Acenaphthenyl-	$C_{12}H_9PO_3H_2$	220	(61)
1,4-Naphthalenebis(methyl-)	1,4-$C_{10}H_6(CH_2PO_3H_2)_2$	229–230	(7)
1,2,3,4-Tetrahydro-5,8-naphthalenebis(methyl-)	5,8-$C_{10}H_{10}(CH_2PO_3H_2)_2$	296–300	(7)
2,3,4-Tri-*O*-acetyl-D-glucopyranose-6-deoxy-6-	$C_{12}H_{17}O_8PO_3H_2 \cdot ?(C_4H_{10}O)$	187–191	(90)

TABLE 7—*Concluded*

Phosphonic Acid	Formula	Melting Point	References
	C_{13} acids		
		°C.	
Aminodiphenylmethyl-	$(C_6H_5)_2C(NH_2)PO_3H_2 \cdot 2H_2O$	232	(160, 161)
Diphenylmethyl-	$(C_6H_5)_2CHPO_3H_2$	169–170	(5)
	C_{14} acids		
α-Benzamidobenzyl-	$C_6H_5CONHCH(C_6H_5)PO_3H_2 \cdot H_2O$	105–107	(162)
1,2,3,4-Tetra-*O*-acetyl-*β*-D-glucopyranose-6-deoxy-6-	$C_{14}H_{19}O_9PO_3H_2 \cdot 2H_2O$	171–172	(90)
	C_{18-21} acids		
Phenylosazone of D-glucopyranose-6-deoxy-6	$C_{18}H_{21}N_4O_3PO_3H_2$	170–172	(90)
Benz[*a*]anthracen-7-ylmethyl-	$C_{19}H_{13}PO_3H_2$	—	(6)
9-Phenyl-9-fluorenyl-	$C_{19}H_{13}PO_3H_2$	268	(92)
o-Methoxy-*α*,*α*-diphenylbenzyl-	*o*-$CH_3OC_6H_4C(C_6H_5)_2PO_3H_2$	239–240	(92)
12-Methylbenz[*a*]anthracen-7-ylmethyl-	$C_{20}H_{15}PO_3H_2$	—	(6)
o-Methyl-*α*,*α*-diphenylbenzyl-	*o*-$CH_3C_6H_4C(C_6H_5)_2PO_3H_2$	264	(92)
α,*α*-Di-*p*-tolylbenzyl-	$C_6H_5C(p\text{-}CH_3C_6H_4)_2PO_3H_2$	272–273	(92)
Tri-*p*-tolylemethyl-	$(p\text{-}CH_3C_6H_4)_3CPO_3H_2$	262–264	(92)

* No analyses or proof of orientation on this compound.

the activity of such well-known toxic agents as tetraethyl pyrophosphate (TEPP) or diisopropyl phosphorofluoridate (DFP).

Trisodium 3-phosphonopropionate has been found to be an active inhibitor of the succinic dehydrogenase of certain protozoa (224, 225). Trisodium arsonoacetate also inhibits the dehydrogenase in these protozoa. Both the arsono and phosphono compounds probably act in a similar manner to sodium malonate, a strong inhibitor of succinic dehydrogenase. Neither the succinic dehydrogenase of rat tissue (224) nor the succinic oxidase of mouse liver (235) was inhibited by the phosphono or arsono compound.

In addition to their antibacterial activity and their effect on isolated enzyme systems, phosphonic acids have been tested as plant auxins. One such series of compounds comprised 1-naphthylmethylphosphonic acid, 1-naphthalenehydroxymethylphosphonic acid, and a mixture of 1,2,3,4-tetrahydro-5(and6)-naphthylmethylphosphonic acids (60). Another series consisted of 1-acenaphthenylphosphonic acid and 1-acenaphthenol-1-phosphonic acid (61). All of these compounds were found to have marked activity in various plants. The compounds were stimulatory in very dilute solution, but markedly toxic in more concentrated solution (182). Other workers, however, have found 1-naphthylmethylphosphonic acid to be only slightly active as a plant-growth regulator (236).

Examples of another type of phosphonic acid, analogous to the chlorophenoxyacetic acids which are known to have plant-growth-regulating activity, have recently been prepared (153, 154). These were synthesized by condensing either

TABLE 8

Aromatic and heterocyclic phosphonic acids

Phosphonic Acid	Formula	Melting Point	References
Compounds containing halogens			
		°*C.*	
o-Bromophenyl-	*o*-$\mathrm{BrC_6H_4PO_3H_2}$	199–201	(24, 68, 69)
o-Chlorophenyl-	*o*-$\mathrm{ClC_6H_4PO_3H_2}$	186.5–188	(44, 67, 133, 144, 145)
o-Fluorophenyl-	*o*-$\mathrm{FC_6H_4PO_3H_2}$	146–149	(65, 84)
m-Fluorophenyl-	*m*-$\mathrm{FC_6H_4PO_3H_2}$	129–130	(133)
p-Fluorophenyl-	*p*-$\mathrm{FC_6H_4PO_3H_2}$	125–127	(38, 133)
o-Iodophenyl-	*o*-$\mathrm{IC_6H_4PO_3H_2}$	219–222	(84)
Compounds containing alkyl groups			
6-Bromo-*m*-tolyl-	2-Br-5-$\mathrm{CH_3C_6H_3PO_3H_2}$	199–203	(84)
p-*tert*-Butylphenyl-	*p*-$\mathrm{(CH_3)_3CC_6H_4PO_3H_2}$	199–200	(132)
p-α-Chlorotolyl-	*p*-$\mathrm{ClCH_2C_6H_4PO_3H_2}$	161	(155)
o-Ethylphenyl-	*o*-$\mathrm{C_2H_5C_6H_4PO_3H_2}$	145.5–147	(16, 79)
m-Ethylphenyl-	*m*-$\mathrm{C_2H_5C_6H_4PO_3H_2}$	128–129.5	(16, 79, 130)
3,4-Xylyl-*	3,4-$\mathrm{(CH_3)_2C_6H_3PO_3H_2}$	150–151.5	(144, 145)
Phenols and ethers			
3-Chloro-4-methoxyphenyl-	3-Cl-4-$\mathrm{CH_3OC_6H_3PO_3H_2}$	192	(146, 237)
p-(Ethylthio)phenyl-	*p*-$\mathrm{C_2H_5SC_6H_4PO_3H_2}$	159–160	(38)
m-Hydroxyphenyl-	*m*-$\mathrm{HOC_6H_4PO_3H_2}$	226–229	(68)
p-Hydroxyphenyl-	*p*-$\mathrm{HOC_6H_4PO_3H_2}$	178	(24, 68)
o-Methoxyphenyl-	*o*-$\mathrm{CH_3OC_6H_4PO_3H_2}$	215†	(24, 65, 84)
3,4-Methylenedioxyphenyl-	3,4-$\mathrm{CH_2O_2C_6H_3PO_3H_2}$	160–161	(38)
Amino and azo compounds			
3-Amino-4-bromophenyl-	3-$\mathrm{H_2N}$-4-$\mathrm{BrC_6H_3PO_3H_2}$	>280 (d.)	(24)
4-Amino-2-chlorophenyl-	4-$\mathrm{H_2N}$-2-$\mathrm{ClC_6H_3PO_3H_2}$	>200†	(84)
p-(2-Aminoethoxy)phenyl-	*p*-$\mathrm{H_2NCH_2CH_2OC_6H_4PO_3H_2}$	>300	(69)
4-Amino-2-hydroxyphenyl-	4-$\mathrm{H_2N}$-2-$\mathrm{HOC_6H_3PO_3H_2}$	210–212	(70)
4-Amino-2-methoxyphenyl-	4-$\mathrm{H_2N}$-2-$\mathrm{CH_3OC_6H_3PO_3H_2}$	212–214	(70)
o-Aminophenyl-	*o*-$\mathrm{H_2NC_6H_4PO_3H_2}$	199–200	(68)
5-Benzimidazolyl-	$\mathrm{C_7H_5N_2PO_3H_2}$	>250	(37)
6-Benzoxazolyl-	3,4-$\mathrm{CH(O)(N)C_6H_3PO_3H_2}$	204–205	(37)
m-(Butylamino)phenyl-	*m*-$\mathrm{C_4H_9NHC_6H_4PO_3H_2}$	198–201	(69)
p-(*p*-Diethylaminophenylazo)-phenyl-	*p*-[*p*-$\mathrm{(C_2H_5)_2NC_6H_4N_2]C_6H_4PO_3H_2}$	—	(136)
p-(*p*-Dimethylaminophenylazo)-phenyl-	*p*-[*p*-$\mathrm{(CH_3)_2NC_6H_4N_2]C_6H_4PO_3H_2}$	—	(121, 136)
m-(Ethylamino)phenyl-	*m*-$\mathrm{C_2H_5NHC_6H_4PO_3H_2}$	238–241	(69)
m-Hydrazinophenyl-	*m*-$\mathrm{H_2NNHC_6H_4PO_3H_2}$	>248	(69)
p-Hydrazinophenyl-	*p*-$\mathrm{H_2NNHC_6H_4PO_3H_2}$	>212	(69)
p-(2-Hydroxyethylnitrosoamino)-phenyl-	*p*-$\mathrm{HOCH_2CH_2N(NO)C_6H_4PO_3H_2}$	>140 (d.)	(69)
m-(Methylamino)phenyl-	*m*-$\mathrm{CH_3NHC_6H_4PO_3H_2}$	226.5–228.5	(69)
p-(Methylamino)phenyl-	*p*-$\mathrm{CH_3NHC_6H_4PO_3H_2}$	177.5–179.5	(69)
2-Methyl-5-benzimidazolyl-	2-$\mathrm{CH_3C_7H_4N_2PO_3H_2}$	>320	(37)
p-(Propylamino)phenyl-, hydrochloride	*p*-$\mathrm{C_3H_7NHC_6H_4PO_3H_2 \cdot HCl}$	180.5–183.5	(69)
Tetracovalent sulfur compounds			
p-Sulfamylphenyl-	*p*-$\mathrm{H_2NSO_2C_6H_4PO_3H_2}$	224–225	(67)
p-(Ethylsulfonyl)phenyl-	*p*-$\mathrm{C_2H_5SO_2C_6H_4PO_3H_2}$	177–178	(38)

TABLE 8—*Concluded*

Phosphonic Acid	Formula	Melting Point	References
	Nitro compounds		
		°*C.*	
4-Anilino-3-nitrophenyl-	4-C_6H_5NH-3-$O_2NC_6H_3PO_3H_2$	—	(66)
2-Bromo-4-nitrophenyl-	2-Br-4-$O_2NC_6H_3PO_3H_2$	217–220	(24)
2-Bromo-5-nitrophenyl-	2-Br-5-$O_2NC_6H_3PO_3H_2 \cdot H_2O$	>230 (d.)	(84)
2-Chloro-4-nitrophenyl-	2-Cl-4-$O_2NC_6H_3PO_3H_2$	221.5–224	(84)
2-Hydroxy-4-nitrophenyl-	2-HO-4-$O_2NC_6H_3PO_3H_2$	202–204	(70)
3-Hydroxy-4-nitrophenyl-	3-HO-4-$O_2NC_6H_3PO_3H_2$	201–202	(37)
2-Methoxy-4-nitrophenyl-	2-CH_3O-4-$O_2NC_6H_3PO_3H_2 \cdot H_2O$	226.5–227.5	(84)
p-(*p*-Nitrophenoxy)phenyl-	*p*-(*p*-$O_2NC_6H_4O)C_6H_4PO_3H_2$	288	(155)
o-Nitrophenyl-	*o*-$O_2NC_6H_4PO_3H_2$	200–203	(80)
p-Nitrophenyl-	*p*-$O_2NC_6H_4PO_3H_2$	197–198	(67, 7
3-Nitro-4-(*p*-toluidino)phenyl-	4-(*p*-$CH_3C_6H_4NH$)-3-$O_2NC_6H_3PO_3H_2$	—	(66)
	Naphthalene derivatives		
4-Amino-1-naphthyl-	4-H_2N-1-$C_{10}H_6PO_3H_2$	170 (d.)	(136)
2,6(or 7)-Naphthylenedi-	2,6(or 7)-$C_{10}H_6(PO_3H_2)_2$	338–345	(144, 145)
4-Nitro-1-naphthyl	4-O_2N-1-$C_{10}H_6PO_3H_2$	220 (d.)	(136)
Sodium trihydrogen 3,3′-(4,4′-biphenylenebisazo)bis(4-amino-1-naphthylphosphonate)	$C_{32}H_{25}N_6NaO_6P_2$		(136)
	Biphenyl and other polynuclear hydrocarbon derivatives		
3,3′-Biphenyldi-	3,3′-$(C_6H_4C_6H_4)(PO_3H_2)_2$	246–252	(76)
4,4′-Biphenyldi-	4,4′-$(C_6H_4C_6H_4)(PO_3H_2)_2$	>300	(76)
2-Biphenylyl-	2-$C_6H_5C_6H_4PO_3H_2$	203–205	(44, 102)
4-Biphenylyl-	4-$C_6H_5C_6H_4PO_3H_2$	218–220	(102)
9-Phenanthryl-	9-$C_{14}H_9PO_3H_2$	228–230	(173, 174)
3-Pyrenyl-	3-$C_{16}H_9PO_3H_2$	233–234	(174)
	Heterocyclic compounds		
4-Methyl-2-quinolyl-	4-CH_3-2-$C_9H_5NPO_3H_2$	>300	(45)
2-Quinolyl-	2-$C_9H_6NPO_3H_2 \cdot H_2O$	>300	(45)

* Orientation uncertain.

† Approximate melting point, since the melting point varies with the rate of heating.

sodium phenoxide or various chlorine-substituted sodium phenoxides with diethyl iodomethylphosphonate to yield ethyl hydrogen phenoxymethylphosphonates. Hydrolysis of the acid esters with hydrochloric acid gave the free acids. Ethyl hydrogen 2,4-dichlorophenoxymethylphosphonate is reported to have slight auxin activity in the split pea and the pea epicotyl tests (89). With wheat seedlings, sodium ethyl 2-chlorophenoxymethylphosphonate and sodium ethyl 2,4-dichlorophenoxymethylphosphonates possessed slight growth-promoting properties. Disodium methylphosphonate in low concentration was found to markedly depress the dry weight of the tops of rape seedlings. In view of the commercial value of disodium methylarsonate as a selective herbicide, the corresponding phosphonate should obviously be further investigated.

The diammonium salt of 12-methylbenz[*a*]anthracen-7-ylmethylphosphonic acid is carcinogenic (6).

VI. Tables of New Phosphonic Acids

Table 7 lists aliphatic and alicyclic phosphonic acids, while table 8 presents aromatic and heterocyclic phosphonic acids.

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COMPARISON OF PHENANTHRIDINE WITH OTHER AZA-AROMATIC HETEROCYCLES

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I. INTRODUCTION

Six-membered nitrogen heterocycles having a formal set of conjugated double bonds occupy a position of prime importance in organic chemistry. Not only do these heterocycles undergo a variety of reactions, but also these systems exhibit a broad spectrum of physiological properties. As they are isosteric with the corresponding aromatic carbocycles, these pyridinoid hydrocarbons may be designated as aza-aromatic heterocycles to stress their similarity to benzenoid hydrocarbons in both reactivity and structure. It is to be expected, however, that the cyclic nitrogen atom will endow aza-aromatic systems with distinguishing properties. These include basicity and a more pronounced proneness to attack by basic reagents. Moreover, the diminished symmetry of the pyridinoid ring allows the existence of more isomers; for example, there are three monosubstituted pyridines. The voluminous literature on aza-aromatic heterocycles attests to the chemical versatility of these systems.

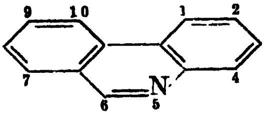
Although there are several monographs that consider in detail the known chemistry of individual heterocycles (89, 272), there exists no comprehensive correlation of the chemistry of aza-aromatic heterocycles as a whole. It is the purpose of this review to compare the analogous chemistry of these aza-aromatic heterocycles and their characteristic derivatives in terms of our present experimental and theoretical knowledge. Modern concepts of molecular structure will be invoked in synthesizing a rational view of aza-aromatic character. The discussion will be largely limited to the monoaza-aromatic heterocycles: pyridine, quinoline, isoquinoline, acridine, and phenanthridine. The behavior to be expected of polyaza-aromatic systems such as quinoxaline and triazine usually involves a reasonable extrapolation of the chemistry of the monoaza-aromatic systems. Five- and seven-membered nitrogen heterocycles such as pyrrole and azepine will not be considered.

Phenanthridine, a nitrogen isoster of phenanthrene, is taken as the focal point of these considerations. There are several valid reasons for this. First, there has recently been a revival of interest in the fundamental chemistry of the phenanthridine system. Despite the large number of phenanthridine derivatives prepared by the cyclization of biphenyl derivatives (249), little progress previously had been made in the substitutional chemistry of this nucleus. In fact, the nitration of phenanthridine, first reported in 1932 (196), gave rise to mononitrophenanthridines which were not identified until 1952 (57). In addition, the direct bromination of phenanthridine has been accomplished only recently (111). By consideration of the known behavior of other heterocycles, the remaining gaps in the knowledge of phenanthridine chemistry will become more apparent.

Second, the discovery of the trypanocidal potency of certain phenanthridine derivatives (197) and their general bacteriostatic properties (8) has given the phenanthridine system a new-found physiological importance. Third, since its molecular asymmetry presents nine nonequivalent positions for substitution, phenanthridine may subject any theory of substitution to a more rigorous test. Factors determining the preferred site of substitution may be more carefully evaluated with such a complex system.

In addition to the discussion of phenanthridine in relation to other aza-aromatic heterocycles, there is included in tables 5 to 11 a compilation of the known phenanthridine derivatives. This list of compounds is intended to supplement that given in a previous review (249). This latter article contains an adequate survey of phenanthridine chemistry up to 1950, but generally lists only those phenanthridines prepared by the cyclization of 2-acylaminobiphenyls. A more detailed and interpretative discussion, but lacking a tabulation of compounds, has also appeared (263). The present list attempts to cover the literature from 1884 through 1955, although some more recent articles are included

The numbering systems of the nitrogen heterocycles appearing in this review are in accord with usages of *Chemical Abstracts*. Both the *Ring Index* (207) and *Chemical Abstracts* (since 1937) advocate the numbering system for phenanthridine shown in formula I. The system employed previous to 1937 and still favored by foreign journals is given in formula II. This system has the merit of paralleling that of phenanthrene. Nevertheless, for the sake of conforming to American usage, system I will be employed throughout this review.



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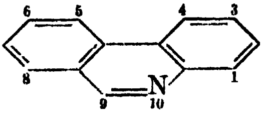


II

II. AROMATICITY

The fact that chemical knowledge gathered from the study of aliphatic compounds failed to account for the behavior of aromatic systems has been termed historically the "benzene problem." Eminent chemists from almost the beginning of organic chemistry have been intrigued by the unusual stability of these systems and the preference for substitution rather than addition reactions. It has been long recognized, moreover, that certain cyclic nitrogen compounds such as pyridine also possessed this aromatic character. Thus an analogous "pyridine problem" arose. Here, indeed, the experimental facts were even more puzzling. Not only did pyridine derivatives have unique properties such as basicity, but they underwent reactions with sodium amide and potassium hydroxide (61, 63) with a facility unknown to benzene.

Preëlectronic interpretations of the aromatic character of pyridine closely paralleled the explanations proposed for the behavior of benzene. Korner and Dewar (85) proposed a cyclic structure of alternate oscillating double bonds analogous to Kekulé's representation of benzene (144), and shortly afterwards Riedel (222) supported a Dewar structure containing a para bond between the nitrogen and the gamma carbon. This was followed by a centric structure advanced by Bamberger (20). However, perhaps the representation of pyridine most in accord with modern views was that based on Thiele's theory of partial valences (250). It would be overdemanding to expect that a fully satisfying solution to the problem of aromaticity would predate the knowledge of molecular structure and the nature of chemical bonding. Thus, the subsequent formulation of the electronic theory of valence (152, 171) coupled with newer experimental data gave a firm foundation to the more satisfying views which were to follow.

The discovery of the electron and the postulation of its role in chemical bonding laid the stage for a more intimate understanding of chemical behavior. The statement by de Broglie (41) that small particles such as electrons should exhibit wave properties was experimentally confirmed by Davisson and Germer (72), who showed that an electron beam could indeed be diffracted. Schrödinger (232) and Heisenberg (127) independently began to give mathematical expression to these wave properties of matter. Heisenberg's uncertainty principle postulated that both the energy and the position of an electron could not be determined exactly. The position of an electron in an atomic field was therefore expressed as a probability function, the results of which were expressed as electron density patterns. Application of these quantum-mechanical calculations to such simple systems as the hydrogen molecule permits the observed energy of the chemical bond to be duplicated to a high degree (134), but extension to larger molecules in a similar manner thus far is unfeasible owing to mathematical complexities. Consequently, the search has been undertaken to develop simplified, approximate methods for estimating molecular energies which would still yield useful information. In the study of aromatic systems factors to be unified and rationalized include: the inherent stability of such systems; the orientation of substituting species; the relative reactivities of related aromatic compounds. Quantum-mechanical calculations have made gratifying progress in attaining these goals, but certain facets of present theory are still quite unsatisfactory. Often the divergence of theoretical predictions and experimental results indicates the importance of certain factors neglected in the simplified treatment and stresses the fact that theory and experiment must keep close company if they are to be mutually helpful.

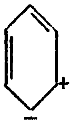
Two approximate methods of treating aromatic compounds such as benzene and pyridine are the valence-bond method and the molecular orbital method.

Both methods have commendable features, but they are different approaches to the same problem. Neither is intrinsically a more accurate description of the molecule, but in certain instances one method may prove more convenient than the other.

For the organic chemist the valence-bond method has the advantage of beginning with the classical, preëlectronic valence formulae and treating them according to wave-mechanical principles. In the approach of Hückel (133) and of Pauling and Wheland (209) a fair approximation of the molecular wave function (Ψ) for benzene was found to be a linear combination of the two Kekulé (ψ_{K_1}, ψ_{K_2}) and the three Dewar structures ($\psi_{D_1}, \psi_{D_2}, \psi_{D_3}$).

$$\Psi = C_1(\psi_{K_1} + \psi_{K_2}) + C_2(\psi_{D_1} + \psi_{D_2} + \psi_{D_3})$$

This set of valence-bond formulae is a complete but not a unique set, as others could be used. Solution of the wave equation tends to be more complicated, since one employs many-electron functions and takes account of electron spin. The result is a unique structure of lowered energy, difficult to express in common structural symbols, but one whose nature can be judged from coefficients (C_1 and C_2) of the contributing structures. There are other ionic structures which do not contribute significantly to the ground state of benzene (III) (and hence may be neglected), but are important in pyridine (IV).



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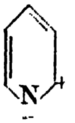


IV

Invoking such ionic structures is useful in explaining the chemical reactivity of nitrogen heterocycles. In this regard, Daudel (71) has carried out a valence-bond treatment of pyridine.

The molecular orbital approximation assumes that the atoms composing the molecule of benzene are arranged as they are in the final molecule. The electrons constituting the skeletal framework of the molecule (σ-electrons) are then fed in. Owing to the geometry of these bonds, little interaction other than covalent-bond formation will take place. However, since the carbon atoms have formed a planar hexagon by assuming sp^2 hybridization, each carbon atom has a p orbital extending above and below the plane of the ring. Since these p orbitals overlap, they interact to form three pi orbitals of lower energy and three of higher. Hence the six remaining electrons upon being fed in will occupy the three lowest-lying molecular pi orbitals. The diminution of energy upon the overlapping of the p orbitals is explained by the delocalization of the p-electron in a pi orbital spread out above and below the ring (68). By the application of the so-called "π-electron approximation," the energy calculations consider only the stabilization obtained by the delocalization of six π-electrons in three molecular orbitals. Hence the wave function Ψ is considered to be:

$$\Psi = \sum^{6} C_n \psi_n$$

As in the wave-particle in a box, the energy of the electron is diminished by increasing the positional latitude of the particle. The results of molecular orbital calculations on such systems are considerably simpler, but they do not lead to any structural formulae. Instead a molecular diagram giving data on π-electron density, bond order, and free valence is indicated. The avoidance of classical molecular formulae is a merit of the method, as it obviates the often misunderstood notion of resonance hybrids. Nevertheless, the enlightened use of valence-bond structures is quite advantageous in certain qualitative considerations. Semiquantitative calculations, on the other hand, are more readily made by means of the molecular orbital method.

A close consideration of the treatment of the pyridine molecule by the method of molecular orbitals will be given below. The utility, scope, and limitations of such calculations are not often stressed. Consequently, it is important that organic chemists be aware of the approximations involved and the dependability of such calculations.

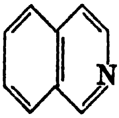
III. Theoretical Views of the Chemistry of Aza-aromatic Systems

A. GENERAL CONSIDERATIONS

An adequate theoretical treatment of aza-aromatic heterocycles must rationalize not only the stability of the ring system but the different orientations of substitution encountered when cationic, anionic, and free-radical reagents are employed. Moreover, the basicity and dipole moments of these systems must be accounted for.

B. BOND FIXATION

As a consequence of the electronic theory of valence it was realized that the basicity of these nitrogen compounds could be due to the unshared electron pair on the nitrogen and that the dipole moment was a manifestation of the electronegativity difference between carbon and nitrogen. Prior to quantum-mechanical treatment of these systems, previous attempts to rationalize reactivity have been based on the concept of "static bonds" in these heterocycles. For example, such proposed formulae for isoquinoline were



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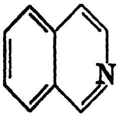
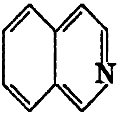


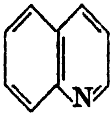
VI



VII

and by chemical reactivity V was adjudged a better representation of isoquinoline than VII, since certain anionic reagents added to the system in a 1,2 rather than a 2,3 manner. VI was considered less satisfactory than V, because according to the Fries rule, VI had only one fully aromatic ring. A classical application of the "static bond" concept is the work of Renshaw, Friedman, and Gajewski (221), who coupled the known aminoquinolines with diazonium compounds.

Assuming that coupling would occur ortho to the amino group only if a double bond intervened, or para if two double bonds were present, these workers found that the sites of reaction were in accord with Erlenmeyer's structure of quinoline (VIII).



VIII

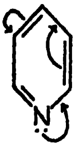
However, the fact that quinoline does indeed have resonance energy (69 kcal. per mole) means that other resonance structures make appreciable contributions to the resonance hybrid. Even if the Erlenmeyer structure were to be the largest single contributor of the linear combination function (i.e., that its ψ would have the largest coefficient), the delocalization or resonance energy would make the resulting unique structure of still lower energy.

Another related approach to the rationalization of the chemical behavior of nitrogen heterocycles has been forwarded by Bergstrom (31). Extending Franklin's ammonia system of compounds, Bergstrom considered the C=N linkage as an ammono aldehyde and hence viewed quinoline as a cyclic ammono aldehyde ether in this system of compounds. All the addition reactions to the azomethine linkage could be correlated with the behavior of aldehydes in similar cases. Derivatives substituted in the alpha position, such as amino, halo, hydroxyl, and methyl, could be compared with amides, acid halides, acids, and methyl ketones. Explanation of similar behavior of the gamma, but not the beta, position rested upon Fuson's principle of vinylogy (106) by which the gamma position would be a vinylogous alpha position. This implicitly assumes bond fixation to the positions represented by Erlenmeyer's formula (VIII).

These views give a fair understanding of chemical behavior but do not take cognizance of modern advances in molecular structure. Besides, the use of chemical reactivity to determine electronic configurations is quite unsatisfactory in aromatic systems, since the molecule will be perturbed by different reagents to varying degrees.

C. QUANTUM-MECHANICAL TREATMENT OF AZA-AROMATIC HETEROCYCLES

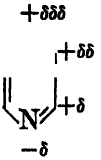
The modern concept of aromaticity as evolved from quantum-mechanical considerations is readily extrapolated to heterocycles such as pyridine, quinoline, and phenanthridine. Owing to the presence of the nitrogen, certain changes must be made in the treatment. The most apparent property distinguishing these compounds from carbocycles is basicity. This stems from the unshared pair of sp^2 hybridized electrons on the nitrogen. Since this orbital extends out from the nitrogen in the plane of the ring (sigma orbital), it cannot overlap with the π-electron cloud which has a node in the plane of the ring. This is theoretically significant, because electromeric interactions have been suggested (16) whereby this electron pair would enhance the electron density at the beta position (IX).



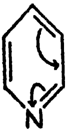
IX

However, the nonoverlapping or orthogonality of the sigma and pi orbitals mitigates against such interactions. Another consequence of this orthogonality is that fixation of a proton on the nitrogen will disturb the pi cloud only by increasing the effective electronegativity of the nitrogen atom. This point is made because the reduced reactivity of pyridine is often explained (198) in terms of the positive-pole pyridinium ion present in acid solution, analogous to the anilinium ion. Such a view neglects the difference in electronic shifts in forming these two cations. This electronic difference is reflected in the unlike behavior of aniline and its ion. On the other hand, pyridine appears to give the same orientation as its ion. The anilinium ion has a reduced reactivity, because fixation of a proton on the nitrogen changes hybridization from sp^2 to sp^3 and thus removes the nitrogen p orbital from overlapping with the pi cloud. Calculations suggest that the pyridinium ion (120) will have only a second-order diminution of charge density at the beta position compared with the unprotonated molecule.

A valence-bond view of pyridine and other pyridinoid systems should take account of two electronic effects caused by substituting the CH in benzene by N. First, by the inductive effect the electronegative nitrogen withdraws electrons toward itself by the sigma-bond framework in the order alpha > beta > gamma carbon (X). Second, the pi cloud at the alpha and gamma carbons will be further depleted of π-electrons (XI). It is clear that such heterocycles will have unequal charge distributions. The physical consequence will be the generation of a dipole moment, whereas chemically the pyridine molecule should be quite susceptible to anionic attack at the alpha and gamma positions.



X



XI

The molecular orbital treatment of aza-aromatic heterocycles has been considered by many workers, including Coulson and Longuet-Higgins (177), Dewar (74), Wheland and Pauling (275), and the French school (217). Although the method involves fairly simple calculations and gives interesting results, some rather formidable assumptions make the results subject to certain reservations.

As a trial wave function for the energy calculations of the pyridine molecule the assumption is made that an approximate wave function (Ψ) is that obtained by taking a linear combination of the nitrogen p orbital wave function and the five carbon 2 p orbital wave functions (π-electron approximation):

$$\Psi = C_1\psi_1 + C_2\psi_2 + C_3\psi_3 + C_4\psi_4 + C_5\psi_5 + C_6\psi_6$$

This wave function is substituted in the modified wave equation

$$E = \frac{\int \Psi \mathrm{H} \Psi \, d\tau}{\int \Psi^2 \, d\tau}$$

$$= \frac{\int \left(\sum_{n=1}^{6} C_n\psi_n\right) \mathrm{H} \left(\sum_{n=1}^{6} C_n\psi_n\right) d\tau}{\int \left(\sum_{n=1}^{6} C_n\psi_n\right)^2 d\tau}$$

where E = energy of the system, H = Hamiltonian of the system, and $d\tau$ = spatial increment. This expression is expanded and the integrals obtained are denoted thus:

$$\int \psi_N \mathrm{H} \psi_M \, d\tau = \int \psi_M \mathrm{H} \psi_N \, d\tau = \mathrm{H}_{NM} = \mathrm{H}_{MN}$$

$$\int \psi_N \psi_M \, d\tau = \int \psi_M \psi_N \, d\tau = S_{NM} = S_{MN}$$

The energy equation is then partially differentiated according to each coefficient to give six differential equations, $\partial E/\partial C_n$, $n = 1, 2, \cdots 6$. By the variation theorem (215) a minimization of energy can be obtained by setting each resulting equation equal to zero. The first of the resulting secular equations is

$$C_1(\mathrm{H}_{11} - ES_{11}) + C_2(\mathrm{H}_{12} - ES_{12}) + \cdots + C_6(\mathrm{H}_{16} - ES_{16}) = 0$$

Now, in order to simplify solution of these equations the following assumptions are imposed:

$\mathrm{H}_{NN(N=3,4,5)} = q$ = energy of a carbon 2 p electron localized on a carbon atom (coulomb integral of carbon)

$\mathrm{H}_{NN(N=1)} = q + x\beta$ = energy of electronegative nitrogen atom for its 2 p electron

$\mathrm{H}_{NN(N=2,6)} = q + y\beta$ = energy of 2 p electron of an alpha carbon atom made more electronegative by the adjacent nitrogen atom

$\mathrm{H}_{N,N+1} = \beta$ = resonance integral (nonadjacent = 0)

S_{NN} = 1; for normalized wave function

$S_{NM(N \neq M)}$ = 0; neglect of overlap

Rewriting the equations and using these approximations, one obtains this determinant:

$$\begin{vmatrix} q - E + x\beta & \beta & 0 & 0 & 0 & \beta \\ \beta & q - E + y\beta & \beta & 0 & 0 & 0 \\ 0 & & q - E & \beta & 0 & 0 \\ 0 & & \beta & q - E & \beta & 0 \\ & & 0 & \beta & q - E & \beta \\ \beta & 0 & 0 & 0 & \beta & q - E + y\beta \end{vmatrix} = 0$$

Useful results can be obtained by solving this determinant for the six roots of E expressed in terms of q and β to give the energy levels for the π-electrons of pyridine. However, the two parameters x and y must be assigned values to account for the decreased energy of a coulomb integral of an electronegative atom (β has negative sign). Unfortunately, no perfectly reliable method is known to estimate these values. Therefore, the error introduced by this uncertainty overshadows the other assumptions of the method. Depending upon the values chosen, the calculated π-electron densities of pyridine vary a great deal. This is illustrated by the data given in table 1. The most promising approach to estimating x and y seems to be the calculation of the dipole moment of pyridine by the vector addition of the pi and sigma dipole contributions. With $x = 0.6$ Löwdin (178) obtained a calculated moment of 2.36 D for pyridine, whereas Orgel and coworkers (206) obtained a value of 2.15 D when x was taken as 1.0. In correlating Hammett sigma values with π-electron densities of heterocycles, Jaffe (138) adjusted the value of x to give the best fit of values and found $x = 0.59$ to give good agreement. However, the experimental value of 2.15 D for the dipole moment of pyridine was recently obtained by microwave spectroscopy (73) and this tends to support a value of $x = 1.0$.

The charge densities could be calculated by inserting the three lowest values of E in the secular equations and obtaining the coefficients of the molecular wave functions. Calculations are simplified, however, by using first-order perturbation theory (177). This is especially advantageous with molecules such as

TABLE 1

π-Electron densities of pyridine and values chosen for parameters x and y

Calculated π-Electron Densities in Pyridine				x	y	Reference
N	C_α	C_β	C_γ			
1.59	0.85	0.95	0.82	2.0	0.25	(177)
1.59	0.83	0.96	0.82	2.0	0.2	(275)
1.274	0.946	0.980	0.874	1.0	0.4	(45)
1.327	0.901	0.982	0.910	0.9	0.1	(216)
1.264	0.920	0.983	0.934	0.6	0.0	(226)
1.234	0.909	1.006	0.940	0.6	0.0	(120)
1.190	0.932	0.993	0.958	0.48	0.0	(120)

phenanthridine, where the molecule is treated as a perturbed phenanthrene. As the parent carbocycle has more symmetry, the calculations can be simplified by group theory (94). The error introduced by the use of perturbation methods is well within the uncertainty caused by the estimation of x.

Besides the charge densities of the different atoms in aza-aromatic heterocycles, free-valence and mobile-bond indices can also be calculated. Free valence indicates the bonding tendency of an atom and is roughly linearly related to the polarizability of the atom. Mobile-bond order measures the multiple-bond character of a chemical linkage (68).

The chemical interpretation of these results is summarized thus (177). The assumption is made that all chemical reagents attack the heterocyclic substrate in one of three manners: first, by electrophilic or cationic attack such as nitration; second, by nucleophilic or anionic attack such as amination with potassium amide; or third, by free-radical processes such as phenylation with benzoyl peroxide. Electrophilic reagents will attack the heterocycles at sites of high π-electron density and nucleophilic reagents will seek out positions of low π-electron density. It is believed that free-radical reagents prefer positions having a high free-valence index.

Some interesting conclusions were reached in a study of the charge densities of a series of nitrogen heterocycles. First, the effect of aza substitution on π-electron density diminishes with the distance between the site of substitution and a given atom. Second, the electronic effect of replacing an additional CH by N appears to be additive. Third, the greater the net charge at a position (either + or −), the more reactive it is to a charged reagent (− or +). Fourth, when there is little difference in the charge densities of positions, the polarizabilities of the positions become important.

Although this view of chemical reactivity is valuable, serious objections can be raised to the view that there is an undoubted correlation between calculated electron distribution and the observed chemical behavior. The nitration, bromination, and sulfonation of quinoline point up several weaknesses in this unified approach. For electrophilic attack the calculated charge densities favor $C_8 > C_6 > C_3$. Sulfonation does indeed occur at C_8, but a temperature factor is involved, as C_6 is attacked at higher temperatures (109). In addition, bromination occurs at C_3, although C_8 and C_6 seem more preferable from theory. If there is little difference in reactivity among the three positions, one would expect that the 8- and 6-isomers would also be found, but this is contrary to experiment (156). Finally, nitration occurs mainly at C_5 with less at C_8 (69). These difficulties in utilizing the charge densities of heterocycles to predict sites of substitution have been attributed to the importance of neglected factors.

From this stemmed the realization that changes in electronic configuration required to attain the transition state of the reaction might often be a predominant factor in determining the site of reaction (273). Another aspect, seriously ignored in the charge-density approach, is the specific nature of the reagent. The behavior of quinoline with the three different electrophilic reagents mentioned above illustrates the importance due to the reagent. Until Brown's work

(46, 47), which will be discussed shortly, there was little concern over whether different electrophilic species might vary in their electronic demands upon the aromatic system in the course of reaction. Thus, a complete theoretical treatment of these aza-aromatic heterocycles necessitates consideration of many other factors besides the ground-state charge distribution of the substrate heterocycle. The following discussion will highlight those factors which must be weighed in the synthesis of a satisfactory rationalization of aza-aromatic chemical behavior.

D. TRANSITION-STATE TREATMENT OF AROMATIC SUBSTITUTION

In the transition-state view of chemical reactivity one reflects upon the electronic alterations undergone in the course of reaction. The variation in the energy of a system is considered as the substituting reagent interacts with the aromatic substrate to form a new bond as the old bond of the displaced group is stretched until the group is expelled. It is felt that a high-energy intermediate may be formed, as XIII, with the two transition states (XII and XIV) involved in getting in and out of such a state. The transition state of higher energy will determine the rate of substitution as the reaction proceeds along the reaction coordinate x (figure 1). The energy of activation ($E^{\ddagger}$) is the difference between the energy of the rate-determining transition state (XII or XIV) and that of the ground state of the reagents. If different aromatic carbon atoms are present in a molecule, substitution should occur preferentially at that carbon atom having the lowest $E^{\ddagger}$. One could then make an accurate prediction of preference in aromatic substitution if there were some manner of assessing the energy of the transition state. Owing to the uncertainty in the exact configuration of this transition state, any semiquantitative calculations must be based upon an assumed model for this state.

In substitution reactions occurring at aromatic carbon atoms it is likely that the original sp^2 hybridization is transformed to approximately an sp^3 or tetrahedral configuration (see XIII in figure 1) in the course of reaction. Consequently, Wheland (273) sought to assess the loss of resonance energy of various aromatic

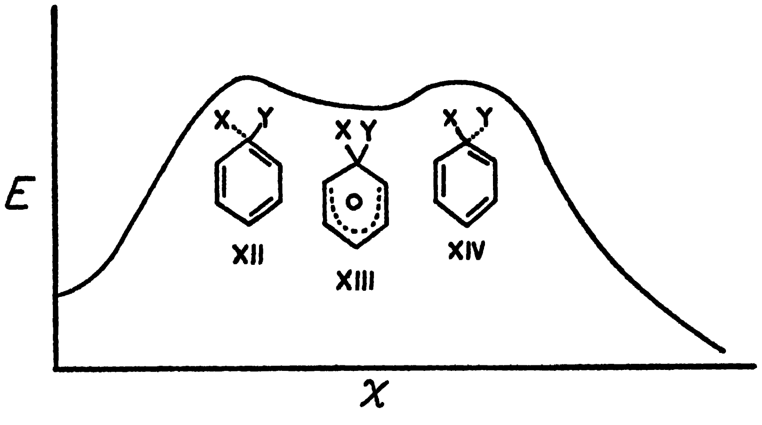
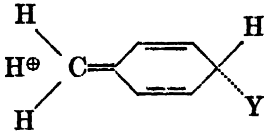


FIG. 1. Variation of the potential energy along the reaction coordinate x

systems by taking such a tetrahedral configuration for the transition-state model. The resonance energy of the tetrahedral model was calculated by the method of molecular orbitals. The resonance energy of the transition state, minus the resonance energy of the ground state obtained in a similar fashion, gave the loss in stabilization (W_B) in going to the transition state. The quantity W_B was taken as an index of $E^{\ddagger}$. Hence, the fact that naphthalene is attacked usually at the 1-position rather than at the 2-position is rationalized by the fact that $W_{B_1} < W_{B_2}$. The method can be applied to electrophilic, nucleophilic, and free-radical attack. Applied to pyridine, the method gave results in general accord with experiment.

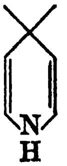
Since the chemical reactivity of aza-aromatic systems can be interpreted either in terms of the ground-state electronic distribution of the heterocycle or the loss of resonance energy in attaining a tetrahedral transition stage, the choice between the two approaches will depend upon the position of the transition state along the reaction coordinate x in figure 1. Both views, however, express extremes of the actual case. As the electrophilic reagent is varied from nitric acid through bromine to sulfuric acid, one might expect a variation in the electronic perturbation of the substrate aromatic compound and hence a shift in the nature of the transition state. Recent studies by Brown and coworkers (46, 47) give experimental foundation for this view and show that the nature of the reagent is important. These workers computed the relative rates of electrophilic substitution of benzene and toluene. With a given reagent a high r(toluene)/r(benzene) was taken as evidence that the transition state in toluene received considerable hyperconjugative aid and hence that it resembled a tetrahedral configuration at the carbon atom attacked (XV).



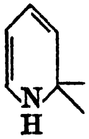
XV

Conversely, a low ratio suggested that the transition state had been reached before a tetrahedral configuration had been attained. As it did not receive hyperconjugative aid, such a reagent was considered more reactive. In a parallel study the meta/para ratios for the attack of the same reagents on toluene were determined. A high value of meta/para suggested that the reagent under consideration had a lower selectivity than one yielding a low meta/para value. In such a manner it was observed that reagents having a high reactivity had a low selectivity (nitric acid), whereas those reagents exhibiting a lower reactivity had a higher selectivity (bromine). (Two exceptions, sulfonation and mercuration, are explicable in terms of proton elimination being the rate-determining step.) Electronically, this correlation may be interpreted thus: The less reactive and more selective electrophilic reagents seem to attain a transition state whose geometry is closely approximated by a tetrahedral configuration at the carbon atom under attack (XIII). Here the factor deciding the site of attack will be the loss of resonance stabilization (i.e., the localization energy) caused by the removal of the p orbital of that carbon atom from the aromatic pi cloud. On the other hand, since the more reactive reagents attain a transition state which is shifted from the tetrahedral model toward the reactants, the site of attack on the aromatic system will depend less on the localization energies and more on the charge densities and autopolarizabilities of the aromatic ground state. Thus, more reactive electrophilic reagents have sufficiently strong cationic centers to polarize the aromatic pi cloud at longer distances and to cause interaction. These looser transition states may consist of a longer new bond or a nonlocalized pi complex.

This relationship between the selectivity and reactivity of chemical reagents seems to be one of wide utility. For example, it seems quite reasonable to extrapolate it to cover nucleophilic attack on aza-aromatic heterocycles as well. Both organolithium and organomagnesium reagents are able to alkylate nitrogen heterocycles such as pyridine and quinoline. Nevertheless, there is a distinct difference of behavior with pyridine. Organolithium reagents attack the alpha position readily (285), whereas allylmagnesium bromide attacks the gamma position with lessened facility (113). An explanation of this difference may be in the following considerations: *n*-Butyllithium is an extremely vigorous nucleophilic reagent, attacking the heterocycles from pyridine to phenanthridine readily even at low temperatures. Allylmagnesium bromide, on the other hand, is a selective nucleophile toward aza-aromatic heterocycles, since it yields only 9 per cent of product with pyridine and gives 81 per cent with acridine. If Brown's correlation on electrophilic attack is extended to nucleophilic attack, one sees that the extremely reactive *n*-butyllithium will attain a transition state shifted toward the ground state, where charge density and autopolarizability favor attack at the 2-position (225). With the less reactive allyl Grignard reagent the transition state should be close to tetrahedral. Invoking Hammond's thermic postulate (121), one can then say that since the latter transition state resembles the allyl-dihydro magnesium bromide product geometrically, it must also resemble the product in energy. Consequently, this product or the dihydro derivative obtained upon hydrolysis is a fair model for the transition state. Hence the respective localization energies for the alpha and gamma positions will become important. Since 1,4-dihydropyridines (XVI) seem to be more stable than 1,2-dihydro derivatives (34) (XVII), the activation (localization) energy may be



XVI



XVII

lower for an attack on the gamma position in pyridine by selective nucleophiles. Other examples of the preference of selective nucleophiles for attack of the gamma position will be mentioned later (Section V,G,4).

IV. FACTORS AFFECTING THE MODE OF ATTACK ON AZA-AROMATIC SYSTEMS

A. SPECIES UNDERGOING ATTACK

The approximate calculations leading to π-electron densities and indices of free valence have already been discussed. It was further stated that the pyridinium ion, present in electrophilic processes, differed in degree and in kind from the "positive-pole" anilinium ion. It is conceded, however, that the charged nature of the pyridinium ion should somewhat hinder electrophilic attack by both the direct field effect and the decrease in the polarizability of the pi cloud. On the other hand, such complexes as the 1-methylpyridinium ion or 1-oxide greatly enhance the reactivity of the alpha and gamma positions toward nucleophilic attack. Here there is increased electronegativity of the hetero atom, further diminishing the electron densities of these positions. No information is available on the effect of quaternization on the facility of attack by free radicals. If the polarizability of the site attacked is a dominating factor, the lessened polarizability of the heterocycle complex should decrease its reactivity.

As detailed discussion will later show, there is often an increase in reactivity to a given reagent as one passes through the series: pyridine, quinoline, isoquinoline, phenanthridine, and acridine. This holds true for electrophilic, nucleophilic, and free-radical attack. In the light of previous comments on the relation between the reactivity of reagents and the nature of the transition state, no one explanation is complete. The possible contributing factors can be summarized. First, the alpha and gamma carbon atoms become more positive as this series is ascended, and the remaining carbon atoms tend toward greater polarizability. This is especially true of dibenzopyridines, where the perturbing nitrogen is more distant. Hence reactivity toward both nucleophilic and electrophilic reagents increases. Second, the localization energy required to remove a p orbital from conjugation with the pi cloud becomes progressively less in this series of heterocycles.

A point should be made concerning the term of "substrate" for the heterocycle. This is arbitrarily applied for convenience. Previously it was said that with a given substrate, a more reactive reagent shifted the transition state toward the ground state and away from a tetrahedral configuration (figure 1). Conversely, it is also true that with a given reagent a more reactive heterocycle will also shift the transition state to the left.

B. ATTACKING SPECIES

Brown's (46, 47) work has shown that the nature of the electrophilic species does indeed determine the electronic demands to be made by the reagent. The correlation is applicable to electrophilic attack on aza-aromatic heterocycles and can be extended to cover nucleophilic attack as well. It would be interesting to determine how the behavior of the fairly stable triphenylmethyl radical compared with the reactive phenyl radical in the reaction with pyridine.

It is well to remember that experimental conditions can alter the nature and reactivity of a species. For example, electrophilic chlorination may occur through a number of species, Cl_2, $H_2OCl^{\oplus}$, HOCl, or $Cl^{\oplus}$, depending upon conditions. As these chlorinating species vary in reactivity, it might be expected that they will attack aza-aromatic systems with various behavior. Also, the species could be changed from electrophilic to free radical in character by the use of higher temperatures or different catalysts.

C. REVERSIBILITY

The reversible nature of some substitution reactions is important in that such reactions tend to obscure the first choice of an attacking species. As a reversal of a substitution reaction will pass through the same reaction configurations as did the forward process (microscopic reversibility), the activation energy of the reverse process will be the activation energy of the forward reaction plus its thermodynamic heat of reaction:

$$E^{\ddagger}_{\text{rev.}} = E^{\ddagger}_{\text{forward}} + \Delta H$$

Reversibility of highly exothermic processes such as nitration is therefore extremely rare. One reported case cites the formation of 4-nitroacenaphthene from 2-nitroacenaphthene (193). Much more common are reversible sulfonations and brominations (109).

Similar to the classical sulfonation of naphthalene, quinoline yields under moderate conditions 8-quinolinesulfonic acid. The reversible nature of this process is evident from the fact that both quinoline and 8-quinolinesulfonic acid yield 6-quinolinesulfonic acid when heated at 300°C. with fuming sulfuric acid (109). Evidently sulfonation and desulfonation occur easily at the 8-position. The activation energy for sulfonation at the 6-position being higher, a higher temperature is required. The desulfonation of the 6-position is so difficult that sulfonation at the 6-position is effectively irreversible. The fact that reversible substitution reactions may take place makes it difficult to correlate halogenation reactions carried out at high temperatures with calculated π-electron densities.

D. SUBSTITUENTS

The electronic behavior of substituents in determining orientation and activation in aromatic systems has been admirably unified by Ingold, Hughes, and others (137). It may be said for heterocyclic systems in general that the presence of strongly activating or deactivating substituents will largely determine the orientation of entering electrophilic groups. In the case of nucleophilic attack, however, these species are still directed to positions alpha or gamma to the nitrogen atom.

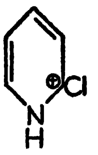
The steric effects of substituents are often important in determining the position attacked by electrophilic species. For example, the nitration of quinoline gives mostly 5-nitroquinoline and some 8-nitroquinoline (69). However, the nitration of 4-methylquinoline gives mostly the 8-isomer (141). Presumably the proximity of the 4-methyl group presents a steric barrier to the attack of the nitronium ion at the 5-position.

E. CATALYSTS

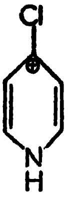
Effectively, a catalyst is an agent which by raising or lowering the activation energy for a reaction retards or accelerates the attack on the molecule. The significance of catalysis in studying the reactivity of aza-aromatic heterocycles is that such assistance can alter the orientation of the attacking species or reactivity of the molecule. This is illustrated by the following examples.

Wibaut's extensive work on the high-temperature halogenation of pyridine and quinoline (129, 277–279) reveals that as the catalyst is changed from iron(II) bromide to copper(I) bromide the orientation changes from predominantly beta to alpha. Presumably the catalyst alters the attacking species from an electrophilic to a free-radical agent (89).

The nucleophilic solvolysis of α- and γ-halo compounds has been found to proceed more readily under acidic than under basic conditions. Evidence adduced by Banks (22) indicates that the protonation of the nitrogen further activates the alpha and gamma positions (XVIII, XIX) to attack by the nucleophilic water molecule.



XVIII



XIX

As might be expected, hydrogenation catalysts show varying behavior. Raney nickel in alcohol preferentially reduces the pyridinoid ring (2), whereas colloidal platinum in acetic acid leads to a completely reduced product (235).

F. TEMPERATURE

The halogenation and nitration of pyridine show a sensitivity of orientation to temperature. At 300°C. with vapor-phase reactants the beta positions are favored. Around 500°C. much decomposition occurs, but attack occurs primarily at the alpha positions (129, 277). Again an explanation proposes a switch from electrophilic to radical attack (274).

The importance of temperature in cases of reversible reactions such as sulfonation has already been pointed out. However, the isomer distribution in such irreversible reactions as nitration is also somewhat sensitive to the reaction temperature. An elevation in temperature will make attack at less reactive positions significantly larger.

G. SOLVENT

The effect of solvent for the displacement reactions in aliphatic systems has been elegantly treated by Hughes and Ingold (134). From these conclusions one would expect some retardation of reaction rate in electrophilic or nucleophilic reactions run in highly polar solvents. The high dielectric properties of such media should diminish the interaction of charged species.

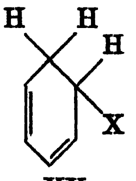
On the other hand, the electrophilic species generated by a given reagent may largely depend upon the solvent. For example, it is felt that electrophilic halogenation may be carried on by species such as HOX, $H_2OX^{\oplus}$, X_2, and $X^{\oplus}$. These species vary in reactivity and the existence of any one of them in a solvent system depends upon the solvating and dielectric properties of the medium. As it is felt that the reactivity of an electrophilic species determines the electronic demands which it will make on an aza-aromatic heterocycle, the solvent employed may influence orientation. An example of this is the nitration of quinoline. With mixed acid the products are 5- and 8-nitroquinolines. However, with lithium nitrate in acetic anhydride 3-nitroquinoline is formed in low yield (76). Previous workers reported that the 7-nitro isomer was formed (15). Acetyl nitrate is felt to be the active agent in the latter case.

V. Chemical Properties

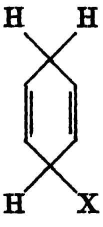
A. SUBSTITUTION REACTIONS

Substitution and addition reactions in aza-aromatic systems tend to overlap. It has been pointed out that a substitution reaction on an aromatic system consists in the formation of a new bond and rupture of the old bond. Such a process may occur concertedly, or there may be formed a tetrahedral intermediate of varying stability (figure 1). Substitution then occurs in two discrete steps. If the intermediate is sufficiently stable, it may be isolated. Subsequent elimination of the original group may then require a distinct chemical reaction. As this intermediate is often isolable in nucleophilic attack on nitrogen heterocycles, the net result is an addition reaction, but as recovery of the aromatic system can be effected, it will be considered as substitution.

Factors contributing to the superior stability of the tetrahedral adduct in aza-aromatic systems might be considered briefly. In the case of benzene the formation of a 1,2 adduct (XX) should require a localization energy of 1.528 β ($\beta \simeq 20$ kcal.), the difference between the resonance energy of benzene and that of the butadiene-type adduct. For a 1,4 intermediate (XXI), however, the conjugation of the formal double bonds is completely disrupted and the localization energy is 2.0 β.

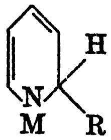


XX

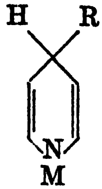


XXI

Addition of organometallic reagents ($R^{\ominus}M^{\oplus}$) to pyridine leads to 1,2 or 1,4 adducts similar to those depicted above for benzene (XXII, XXIII).

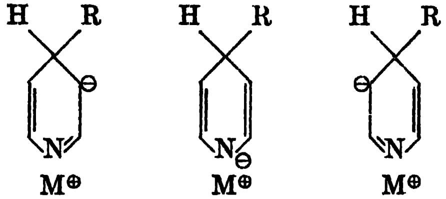


XXII



XXIII

The localization energies for the corresponding pyridine adducts should be less than those given for the benzene molecule. When M is added to the nitrogen, this hetero atom still possesses two electrons which can occupy a *p* orbital. The latter orbital can overlap with the residual pi cloud, somewhat analogous to pyrrole systems. The net result is a smaller loss in resonance energy. Moreover, owing to the highly polar N—M bond, the anion XXIV can contribute even greater stabilization to the adduct.



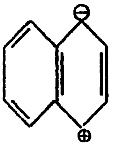
XXIV

B. ELECTROPHILIC SUBSTITUTION

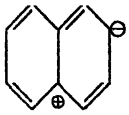
1. *Nitration*

The species considered as the active agent in nitration is the nitronium ion, NO$_2^{\oplus}$ (110). Brown's study indicates that this is a very reactive electrophile of low selectivity. Although the transition state is not very close to the reactants because of the high activation energy of nitration, it seems to be sufficiently shifted from the tetrahedral model to depend more upon the charge density and polarizability of the ground state of the heterocycle.

In the series pyridine < quinoline < isoquinoline < acridine < phenanthridine, the ease of nitration increases significantly. Pyridine gives a 22 per cent yield of 3-nitropyridine when a solution of pyridine in 100 per cent sulfuric acid reacts with potassium nitrate and nitric acid at 300°C. (104, 146). This is contrasted with the quantitative yield of six mononitrophenanthridines obtained when phenanthridine nitrate is dissolved in concentrated sulfuric acid (196). The increasing reactivity of the benzo- and dibenzopyridines can be attributed to the decreasing effect of the hetero nitrogen atom on the more distant benzenoid ring. This leads to an increased polarizability at the carbon atom being nitrated. The isomers formed in the nitration of pyridine, isoquinoline, and acridine are generally in accord with predictions based on calculations of charge density (177). Phenanthridine and quinoline, on the other hand, do not give reasonable agreement. In quinoline it is felt that the more favorable polarizability of the "alpha" positions (C_5 and C_8) overrides the greater charge densities at C_6 and C_3. Dewar (75) suggests that quinoline be considered as a perturbed naphthalene molecule. A valence-bond approach rationalizes the greater polarizability of the "alpha" positions in naphthalene by pointing out that structure XXV has six other contributing structures, whereas structure XXVI has only five (217).

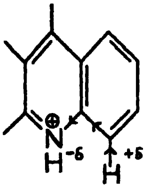


XXV



XXVI

As this enhanced polarizability facilitates nitration, the nitration of quinoline at the 5- and 8-positions is understandable. With the more reactive phenanthridine the tendency toward random substitution is seen in the formation of the 1-, 2-, 3-, 4-, 8-, and 10-nitrophenanthridines (57). The predominance of the 1- and 10-nitrophenanthridines again can be attributed to the greater polarizability of these "alpha" positions. The charge densities favor electrophilic substitution in this order (177): $C_4 > C_{10} > C_8 > C_2 > C_1$, and their failure with nitration has been attributed to their closeness (263). The extremely small amount of 4-nitrophenanthridine formed may be due to the diminished polarizability of the 4-position caused by the adjacent protonated nitrogen (XXVII). This is also reflected in the smaller amount of 8-nitroquinoline and 4-nitroacridine isolated from the nitration of quinoline and acridine, respectively (69, 164, 165).



XXVII

Nitration of these heterocycles with oxides of nitrogen (231) or a mixture of lithium nitrate and acetic anhydride (15) requires further study. Although the latter reagent was reported to give a low yield of 7-nitroquinoline, a recent communication by Dewar and Maitlis (76) claims that it is really 3-nitroquinoline. Certainly the latter isomer would seem more reasonable from charge density predictions.

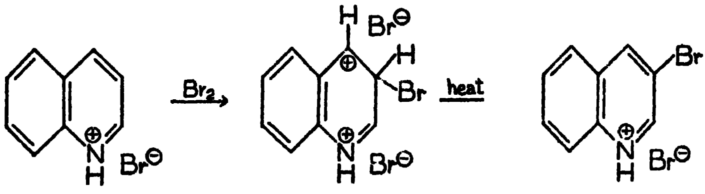
A comprehensive review of the experimental results and theoretical implications of aza-aromatic nitration has been prepared by Schofield (229).

2. Halogenation

Halogenation of aromatic systems occurring under 300°C. and in the presence of Lewis acids is considered to occur by an electrophilic mechanism. The intimate details of the process are not nearly as well known as they are in the case of nitration.

Comparative data on the bromination of these nitrogen bases are quite meager. If bromination accomplished by heating the perbromide hydrobromide is examined, it appears that the facility of bromination does not vary markedly. Pyridine gives only 37 per cent of 3-bromopyridine but also 26 per cent of 3,5-dibromopyridine (181); quinoline yields 62 per cent of the 3-isomer (156); and isoquinoline forms up to 74 per cent of 4-bromoisoquinoline (114). The lack of any sharp difference in reactivity may stem from the fact that in all cases attack is on the deactivated pyridinoid ring. Acridine and phenanthridine have no available positions beta to the nitrogen in the pyridinoid ring. The position assumed by the entering bromine atom might help to elucidate the factors determining the selectivity of bromination. Bromination of acridine with *N*-bromosuccinimide (228) led to small amounts of two isomeric bromoacridines. The unidentified products were thought to be the 2- and 4-isomers. The analogous reaction with phenanthridine gave a 40 per cent yield of 2-bromophenanthridine (111). Recently, 2-bromoacridine and 2,8-dibromoacridine have been obtained by heating acridine with bromine in glacial acetic acid (1).

The orientation in the bromination of quinoline and isoquinoline has long been considered anomalous. As was indicated previously, charge densities would favor attack in the order $C_8 > C_6 > C_3$ for quinoline and $C_5 > C_7 > C_8$ for isoquinoline (177). Preference for the deactivated pyridinoid ring over the benzenoid ring suggests that there are unusual features about halogenation which require further study. It is conceivable that bromine could react with the polar C_3—C_4 bond and thus halogenate the heterocycles by an addition-elimination process (XXVIII to XXX).



XXVIII XXIX XXX

The similar behavior of chlorination (19), iodination (245), and mercuration (253) may be explicable in a parallel fashion.

3. Sulfonation

The sulfonation of these nitrogen heterocycles results in various isomeric sulfonic acids depending upon the strength of oleum and the temperature employed. The reversible nature of sulfonation, previously mentioned, vitiates theoretical predictions of the most likely sites of substitution. Moreover, the reactive nature of the electrophilic sulfur(VI) oxide present in oleum tends to the formation of more isomers. Thus, the sulfonation of quinoline occurs mainly at C_8, but the C_5, C_6, and C_7 positions are also attacked (65, 101, 157). The ease of sulfonation seems to increase in the following order: pyridine < quinoline < isoquinoline < phenanthridine (97, 100, 112). Attempts have been made to sulfonate acridine, but with limited success (162, 163).

There is evidence that the transition state of sulfonation has made much progress along reaction coordinate x in figure 1. Melander (185) has observed that tritium-substituted aromatic systems do show a kinetic isotope effect when sulfonated. This may be interpreted to mean that the step of proton rupture (XIV in figure 1) is rate-determining. Since the transition state is much removed from the ground state, localization energies may be a better criterion for predicting sites of attack than charge densities. Pyridine can be sulfonated at the only feasible position (C_3) under rather stringent conditions. If the lower localization energy of an "alpha" position is recalled, the major attack at C_8 in quinoline, at C_5 in isoquinoline, and probably C_4 in phenanthridine is understandable. The reversal of these sulfonations at more elevated temperatures demonstrates the ready accessibility of the transition state from both directions along the reaction coordinate x.

4. *Mercuration*

The mercuration of aza-aromatic heterocycles is usually carried out in two steps. First, the base and mercury(II) acetate are warmed to yield a complex of two molecules of base with one molecule of the mercury salt. This is probably a Werner-type complex. Upon heating the complex, the heterocycle is mercurated with the elimination of acetic acid (253).

Mercuration is in general a less reactive electrophilic process than nitration or sulfonation. In its reactivity and its orientation in heterocycles, it parallels the behavior of bromination. With pyridine, quinoline, and isoquinoline it attacks the same positions as does bromination. (In the case of quinoline it also attacks the 8-position.) The mercurations of acridine and phenanthridine have not been reported.

As was mentioned under the discussion of bromination, the mercuration may occur by means of an addition-elimination process.

5. *Friedel–Crafts alkylation*

The electrophilic alkylation of these heterocyclic bases has not been accomplished. As with nitrobenzene, the aza-aromatic heterocycles fail in this reaction because of complexation of the catalyst with the hetero nitrogen atom. It is quite possible, however, that alkylation of dibenzopyridine systems could be realized under forcing conditions.

C. NUCLEOPHILIC SUBSTITUTION

1. *Alkylation*

An alkylation procedure of limited utility is the Ladenburg synthesis of alkylpyridines (159). Heating alkyl halide salts of pyridine at 290–300°C. leads to a mixture of 2- and 4-alkylpyridines. Although the mechanism has not been studied, orientation suggests that it proceeds by a nucleophilic or, more likely, a free-radical process.

Reaction of these heterocycles with Grignard reagents ordinarily has been carried out under "forcing" conditions such as the use of dioxane (29) or an autoclave (32). This illustrates the lowered nucleophilicity of ordinary Grignard reagents. It is significant that allylmagnesium bromide reacts readily with phenanthridine, acridine, and quinoxaline in ether solution. The allyl anion is stabilized by resonance; hence this Grignard reagent should have an enhanced polar character (XXXI).

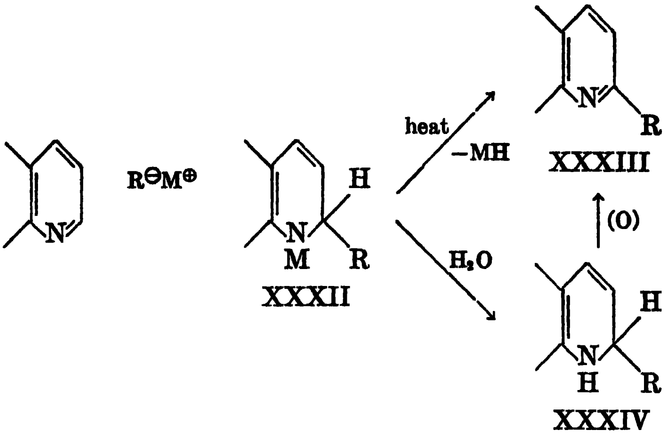
$$\begin{array}{cccc} \mathrm{BrMgCH_2CH{=}CH_2} & \rightleftarrows & \overset{\ominus}{\mathrm{C}}\mathrm{H_2CH{=}CH_2} & + \ \overset{\oplus}{\mathrm{M}}\mathrm{gBr} \\ \mathrm{XXXI} & & \updownarrow & \\ & & \mathrm{CH_2{=}CH}\overset{\ominus}{\mathrm{C}}\mathrm{H_2} & \end{array}$$

With a series of aza-aromatic heterocycles and anils, allylmagnesium bromide gave the following reactivity series: pyridine < quinoline ≃ isoquinoline < phenanthridine ≃ benzalaniline ≃ acridine < quinoxaline < benzophenone anil (112, 113). The selective character of allylmagnesium bromide versus that of *n*-butyllithium in the reaction with pyridine has been discussed previously (Section III,D).

The reaction of Grignard reagents occurs mainly at the alpha positions in quinoline, quinoxaline, isoquinoline, and phenanthridine. In pyridine and acridine the gamma position is attacked. Some of the earlier work has been discredited. Although Bergmann and Rosenthal (29) reported that benzylmagnesium chloride and pyridine gave a small yield of 2-benzylpyridine, repetition of this work by Veer and St. Goldschmidt (255) led to the conclusion that the 4-isomer was formed instead. Parallel studies using allylmagnesium bromide (113) support the work of the latter authors. Likewise, Bergstrom and McAllister (32) reported the preparation of 2-ethylpyridine from ethylmagnesium bromide and pyridine in an autoclave. Recently, 2-ethylpyridine was prepared unambigously (119) and shown to differ from the product of Bergstrom and McAllister. Repetition of the autoclave reaction gave only bipyridines (116).

The most elegant alkylation procedure involves the use of alkyllithium compounds (285). Applicable also to arylation, the reaction proceeds easily at room temperature. The heterocycles pyridine, quinoline, isoquinoline, acridine, and phenanthridine react extremely readily with *n*-butyllithium. The attack occurs predominantly at the alpha position except in acridine, where only the gamma position is available.

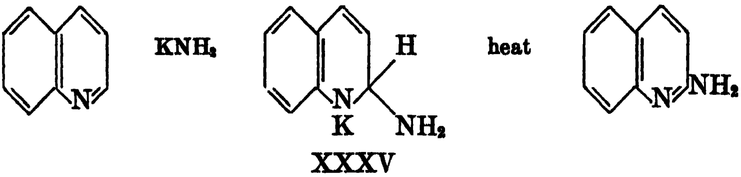
The reaction mechanism of lithium and Grignard reagents seems to involve the nucleophilic attack of the alkyl anion on the heterocycle (or heterocycle complexed with the reagent (224)) at the positions of lowered charge density. The isolable adduct (XXXII) formed may split out the metallic hydride thermally (XXXIII), or the dihydro compound obtained upon hydrolysis may be oxidized (XXXIV):



The factors determining the attack of allylmagnesium bromide at the gamma position of pyridine have been discussed previously (Section III,D). The Grignard reactions carried out under autoclave conditions, however, may well involve free-radical processes.

2. Amination

Aza-aromatic bases react readily with potassium amide to yield amino derivatives with the evolution of hydrogen (161). With pyridine and quinoline both the alpha and gamma derivatives are formed. There seems to be no marked difference in yield among pyridine (82–90 per cent), quinoline (63 per cent), isoquinoline (83 per cent), phenanthridine (90 per cent), and acridine (72 per cent). Data indicate that this process is a nucleophilic attack of the amide anion on the positions of lowest charge density with the expulsion of the hydride ion. The process is thus quite analogous to nucleophilic alkylation.



Bergstrom (30) has obtained experimental evidence for the intermediate adduct (XXXV).

The amide ion is a reactive nucleophile, but less reactive than the hydride or alkyl anion.

3. Hydride-ion reduction

The behavior of a series of aza-aromatic heterocycles towards lithium aluminum hydride has been studied recently by Bohlmann (37). Although no quantitative data were presented, facility of reaction increased in the order pyridine <

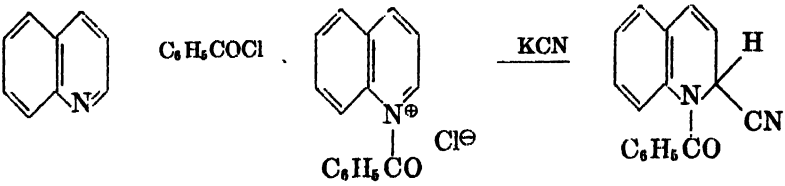
quinoline < quinoxaline < acridine. Interestingly enough, piperidine was formed in 10 per cent yield from pyridine, together with an unstable product behaving like 1,2-dihydropyridine. The product from quinoline was possibly a mixture of 1,2- and 1,4-dihydroquinolines, as two distinct orange-red picrates were isolated. The behavior of phenanthridine with this reagent has been studied independently (284) and 5,6-dihydrophenanthridine was obtained in 74 per cent yield. These data also suggest a dependence of reactivity on the lowered charge density of the alpha and gamma positions, as reaction probably occurs through a nucleophilic attack of the hydride ion. The behavior of lithium aluminum hydride is quite analogous to that of *n*-butyllithium, although the latter seems to be more reactive.

4. Hydroxylation

The nucleophilic hydroxylation of these nitrogen bases by dry potassium hydroxide was discovered by Chichibabin (61). Recently, the reaction was extended to phenanthridine (112). Analogous to amination, hydroxylation occurs through a nucleophilic attack of the hydroxide ion at a position of lowered charge density. The large activation energy of the process is reflected in the high temperatures required (200–300°C.). Amination and hydroxylation probably have as their rate-determining step the expulsion of the hydride ion. The carbon–hydrogen bond energy is 87.3 kcal. per mole, whereas that of a carbon–nitrogen bond and a carbon–oxygen bond are 48.6 and 70.0 kcal. per mole, respectively (208). Judged by the time and temperature, the facility of hydroxylation increases thus: pyridine < quinoline < isoquinoline < phenanthridine. Reaction takes place uniformly at the alpha position.

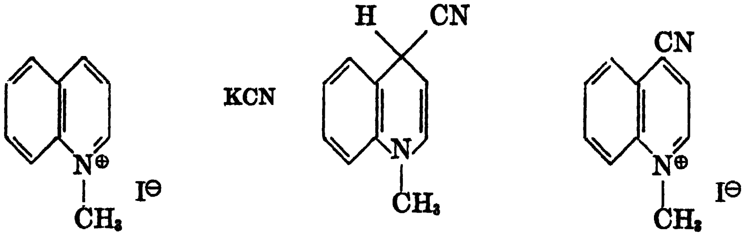
5. Cyanation

Various procedures lead to the nucleophilic attack of cyanide ion on these heterocycles. A general method developed by Reissert (220) has been applied to quinoline, isoquinoline, and phenanthridine (283), but failed with pyridine (219). The procedure involves the reaction of potassium cyanide with the benzoyl chloride complex (XXXVI) of the heterocycles in anhydrous solvents.



XXXVI

The reaction proceeds readily and the cyanide ion attacks the alpha position. This is to be contrasted with the Kaufmann reaction (143), in which treatment of quinoline methiodide with potassium cyanide leads to a dihydro intermediate (XXXVII) oxidizable by iodine to 4-cyanoquinoline methiodide.



XXXVII

Surely attack at either the alpha or the gamma position in quinoline is compatible with nucleophilic cyanation, but the switch in orientation must be considered. The fact that the benzoyl chloride complexes of heterocyclic bases may be used as benzoylating agents (180) suggests a loosely bound complex on the nitrogen (XXXVI). On the other hand, methiodides of heterocyclic bases are not methylating agents under ordinary circumstances. This points to a methyl group intimately bound to the nitrogen. Such a group could create a definite steric barrier to attack at the alpha position, whereas the benzoyl chloride complex might be loose enough to permit access to the alpha position.

Finally, acridine reacts readily with hydrocyanic acid in alcohol to give 9-cyanoacridine (166). Examination of the experimental conditions reveals that the cyanide ion, a rather unreactive nucleophile, requires activation of the heterocycle by quaternization of the nitrogen atom. With the more reactive acridine system such activation is unnecessary.

D. FREE-RADICAL SUBSTITUTION

Admittedly much less is known about the intricacies of free-radical attack (267). However, such processes seem to be involved in surface reactions (catalytic hydrogenation and metal reductions), in reactions at very high temperatures (vapor-phase bromination at 500°C.), and in reactions involving metals or radical sources (sodium metal or peroxides).

1. *Phenylation*

If the polarizability of a position is important, the alpha and the gamma positions should be preferred in radical processes (273). Experiment partially confirms this. When pyridine is phenylated by radicals from benzoyl peroxide or basic benzenediazonium salts (123), all three phenylpyridines are isolated but predominantly the alpha isomer. The reactivity of the phenyl radical may cause a tendency toward random substitution.

2. *Methylation*

Recently, Levy and Szwarc (170) carried out a quantitative study of the interaction between aromatic systems and methyl radicals obtained from the decomposition of acetyl peroxide. No attempt was made to determine the orientation of the methyl groups in the products. Instead, the aromatic systems were assigned relative reactivities towards methyl radicals with benzene taken as

TABLE 2

Relative reactivities of aromatic systems toward methyl radicals (benzene taken as 1)

Carbocycle	Reactivity Index	Heterocycle	Reactivity Index
Naphthalene	22	Pyridine	3
Phenanthrene	27	Quinoline	29
Chrysene	58	Isoquinoline	30
Pyrene	125	Acridine	430
Anthracene	820		

unity. The values given in table 2 were obtained. In general, the aza-aromatic heterocycle is slightly more reactive than its parent carbocycle, but acridine is anomalous in this respect. It was observed that there was a linear relation between the logarithm of the methyl affinities and the singlet-triplet excitation energies of the aromatic systems.

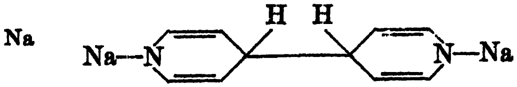
3. Reduction

This discussion embraces those reductions involving a metal coupled with an acid or a base. Modern opinion considers as fiction the importance of "nascent" hydrogen in such reductions. Burton and Ingold (51) have pictured such reductions as occurring on the metal surface as free-radical or nucleophilic transfer of electrons to the pi cloud of the electrophilic molecule. With nitrogen heterocycles the electron-receptive centers would be the alpha and gamma positions. The anion formed will accept protons from the solvent at the position of highest charge density. The pyridinoid ring, once partially disrupted in this manner, tends to becompletely reduced. For an explanation of such nonthermodynamic reductions, the discussion of Hammond (121) should be read.

Sodium and alcohol, and tin and hydrochloric acid, form piperidine, 1,2,3,4-tetrahydroquinoline, and 1,2,3,4-tetrahydroisoquinoline from the respective heterocycles (20, 152, 169). Acridine and phenanthridine are reduced to 9,10-dihydroacridan (118) and 5,6-dihydrophenanthridine (135), respectively.

4. Coupling

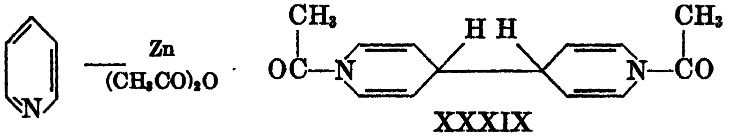
The use of active metals as reducing agents for these heterocycles has led frequently to bimolecular reduction. In the aldehyde analogy of Bergstrom this is equivalent to the pinacol reduction. The reaction occurs with pyridine (91), quinoline (271), acridine (227), and derivatives of isoquinoline (77), but it has not been reported for phenanthridine. At room temperature pyridine seems to couple mainly through the gamma positions (XXXVIII) and to a lesser extent through the alpha positions.



XXXVIII

Presumably such coupling occurs on the metal surface by free radical processes. At higher temperatures 2,3′, 3,3′, and 3,4′ coupling products are also formed, besides polypyridines (236). The behavior of quinoline is different, as it forms mainly the 2,3′ coupling product (271). Acridine yields 9,9′-biacridine (227).

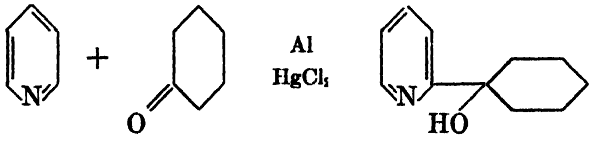
An interesting reaction discovered by Dimroth (84) and extended by Wibaut and Arens (273) is the reductive coupling of pyridine with zinc and acetic anhydride (XXXIX):



XXXIX

The conditions suggest that the acetylpyridinium ions are reduced on the zinc surface by a simultaneous two-electron transfer, analogous to the pinacol reduction.

Recent work (175) has led to a mixed pinacol reduction with pyridine and aliphatic ketones. The predominant product is the 2-isomer (XL), although the amount of the 4-isomer is sometimes significant (251).



XL

5. *High-temperature reactions*

Reactions occurring under stringent conditions of heat and pressure tend toward radical processes. It has been mentioned that vapor-phase bromination (129, 277–279) and coupling indicate that free-radical processes are operative.

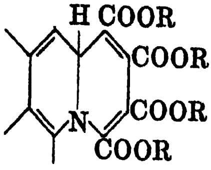
E. ADDITION REACTIONS

1. *Hydrogenation*

Catalytic hydrogenation of these nitrogen bases may occur selectively in the pyridinoid ring. For example, Raney nickel reduction of pyridine (3), quinoline (2), and isoquinoline (108) leads to piperidine, 1,2,3,4-tetrahydroquinoline, and 1,2,3,4-tetrahydroisoquinoline, respectively. Under these conditions acridine yields acridan (7) and phenanthridine forms 5,6-dihydrophenanthridine (135). With platinum and glacial acetic acid the aza-aromatic heterocycles tend to be completely reduced (235). The greater tendency of the pyridinoid ring to reduction may be attributed to its greater electrophilicity when adsorbed on the metal surface.

2. *Reaction with dialkyl acetylenedicarboxylate*

A rather peculiar reaction is undergone by dialkyl acetylenedicarboxylate and pyridine (79), quinoline (78), isoquinoline (80), or phenanthridine (82). Although several labile adducts have been isolated, the accepted structure of the stable adduct is XLI:



XLI

Like anthracene, acridine undergoes a normal Diels–Alder reaction because no alpha position is available (81). The mechanisms of these reactions are not clear, but it is possible that radical processes determine preference for the alpha and gamma positions.

3. *Nitrogen complexes*

Acceptance of the unshared sp^2 electrons on the hetero atom by an atom or cation tends to increase the effective electronegativity of the nitrogen. The resultant effect on the charge density has been considered previously (Section IV,A,E).

a. *N*-Oxides

The action of per acids on these nitrogen heterocycles leads to the formation of *N*-oxides. Careful studies on the ease of formation have not been made, but the action of hydrogen peroxide in acetic acid suggests that phenanthridine may be more difficult to oxidize than quinoline or pyridine (204). In the former case phenanthridone is formed as a by-product (189). This increased resistance may be due to the lower basicity of phenanthridine.

b. Quaternization

The reaction with alkyl halides or dialkyl sulfates occurs with a notable variation in facility. Methyl iodide reacts readily with pyridine, quinoline, and isoquinoline, but acridine and phenanthridine require heating in hot nitrobenzene or benzene for quaternization. As the calculated electron density on the nitrogen increases from pyridine to acridine, one would expect acridine to be more reactive than pyridine. Parallel studies with the quaternization of tertiary alkyl amines show that there is a marked dependence of activation energy on the basicity of the amine (92). The lowered reactivity of phenanthridine can be due to its weak basicity, but not that of acridine (table 3).

TABLE 3

pK_a values for heterocyclic bases at 20°C.

Base	pK_a IN H_2O	pK_a IN 50% ETHANOL
Pyridine	5.23	
Isoquinoline	5.14	
Quinoline	4.94	
Acridine	5.60	4.11
Phenanthridine		3.30

TABLE 4

pK_a values of diaza-aromatic heterocycles at 25°C.

Base	pK_a	Base	pK_a
Quinazoline	3.51	Pyrimidine	1.30
Phthalazine	3.47	Phenazine	1.23
Cinnoline	2.70	Quinoxaline	0.8
Pyridazine	2.33	Pyrazine	0.60

c. Salt formation

The unshared electron pair on the nitrogen can accept a wide variety of Lewis acids, ranging from protons to aluminum chloride. The basicity of these heterocycles toward protons has been of considerable theoretical and physiological interest. Expressed in terms of pK_a for the equilibrium,

$$B: + H^{\oplus} \rightleftarrows BH^{\oplus}$$

$$K_a = \frac{[B:]\,[H^{\oplus}]}{[BH^{\oplus}]}$$

the values are given in table 3 (6). The decrease in basicity in going from pyridine to phenanthridine is opposed to predictions based on charge densities (177). Dyatkina (86) suggests that a change in the carbon–nitrogen resonance integral may be the source of this discrepancy, and Brown and Dewar (45) feel that second-order terms involving the self-polarizability of the nitrogen atom may be important.

The pK_a values of certain diaza-aromatic heterocycles are presented in table 4 (6). Introduction of a second nitrogen atom greatly reduces the base strength.

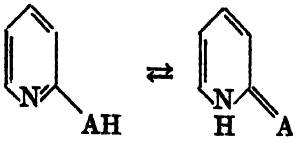
F. RING STABILITY

The thermal stability of these nitrogen heterocycles is reflected in their recovery from the pyrolytic products of soft coal. Both acridine and phenanthridine distil unchanged at around 350°C.

Oxidation of these bases with alkaline potassium permanganate indicates the superior stability of the pyridinoid ring. The resistance of pyridine to oxidation makes it a suitable solvent for oxidation reactions. With quinoline the benzenoid ring is preferentially destroyed, yielding 2,3-pyridinedicarboxylic acid. Isoquinoline is also attacked in the benzenoid ring, leading to 3,4-pyridinedicarboxylic acid. Degradation studies of substituted phenanthridines have yielded phthalic acid (263), but the products from phenanthridine itself have not been reported. The general preservation of the pyridinoid ring may be due to its diminished polarizability. The nature of the attack is somewhat dependent upon the oxidizing agent employed, however.

G. COMPARISON OF CHARACTERISTIC DERIVATIVES

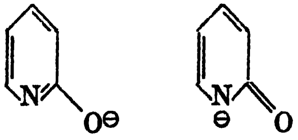
The characteristic behavior of the alpha and gamma derivatives of these heterocycles is a direct consequence of the lowered π-electron density at these positions and hence warrants careful examination. Experimental evidence in the case of the amino, methyl, and hydroxyl derivatives has suggested the possibility of tautomerism (XLII, XLIII).



XLII XLIII

$A = NH, O, CH_2$.

Many researchers have attempted to determine chemically which tautomer is more descriptive of the real state of the molecule. Thus, workers have methylated 2-hydroxypyridine with dimethyl sulfate in basic solution and also with diazomethane. Since the first reagent gave *N*-methyl-2-pyridone and the second 2-methoxypyridine, it was felt that tautomer XLIII is more important in basic solution and that tautomer XLII predominates in neutral solution (186, 218). Such evidence is of no validity, since in basic solution one is probably dealing with the anion (XLIV):



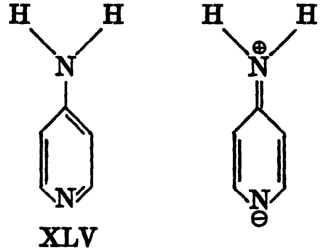
XLIV

The point at which methylation will occur then depends upon how much the anion is deformed in the course of reaction. If little deformation is necessary, the site of highest charge density will be methylated. If much deformation is necessary, the site causing the lesser loss of delocalization energy will be attacked. These considerations stress the unreliability of using chemical methods only to study tautomeric systems.

1. Amino derivatives

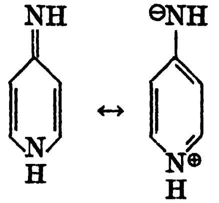
The position of the possible tautomeric equilibrium between the α- or γ-amino tautomer and the imino form has been studied by both chemical and physical means. Besides alkylation experiments similar to those carried out with 2-hydroxypyridine, the behavior of these amines upon diazotization, hydrolysis, and attempted Schiff base formation has been adduced as proof for the existence of one or the other tautomer. All this chemical evidence is subject to objection, as a chemical reaction perturbs the system a great deal. If one tautomer reacts more readily, the existence of a mobile equilibrium will allow the more reactive form to be replenished at the expense of the less reactive one.

Even the physical methods of studying such tautomerism yield ambiguous results in certain instances. Leis and Curran (167) measured the dipole moment of 4-aminopyridine and compared it with that of aniline and pyridine. They ruled out the imino form XLVI in favor of the amino form XLV, as they thought that the former could not account for the high dipole moment.



XLV

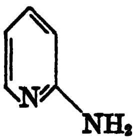
Angyal and Angyal (12) argued, however, that this conclusion did not follow of necessity, as the imino form could have significant dipolar character (XLVI).



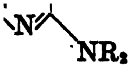
XLVI

That imines can have high dipole moments was demonstrated by the value obtained from 1,4-dihydro-4-imino-1-methylquinoline (5.1 D), as compared with that of 4-aminoquinoline (4.4 D).

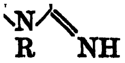
The observation of the shifts obtained in the ultraviolet spectra of aminopyridines, aminoquinolines, and aminoisoquinolines in acidic and basic solutions led Steck and Ewing (239) to state that the α- and γ-amino derivatives existed in the imino form. This conclusion was based upon the assumption that nuclear protonation should cause a bathochromic shift, whereas protonation of the amino group should cause a hypsochromic shift in the ultraviolet spectra. Since there was little appreciable bathochromic shift of the spectra of the amines in acid solution, it was concluded that the hetero nitrogen was largely saturated. The pitfalls of conclusions from spectral shifts are discussed in a careful fashion by Angyal and Angyal (12). A more reliable criterion is that of the similarity of the spectra of the amines to that of *N*-methylated derivatives. Such a comparison was carried out by Anderson and Seeger (10) with the 2- and 4-aminopyridines. The close similarity of the spectrum of 2-aminopyridine (XLVII) to that of 2-methylamino- and 2-dimethylaminopyridines (XLVIII) and its dissimilarity to that of *N*-methylpyridonimine (XLIX) indicate that 2-aminopyridine is in the amino form.



XLVII

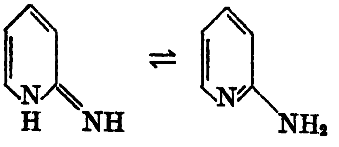


XLVIII



XLIX

Moreover, no evidence could be obtained for any tautomeric equilibrium. The same conclusions were reached with 4-aminopyridine. Angyal and Angyal (12) calculated that the equilibrium constant for the tautomeric system (L, LI)



L LI

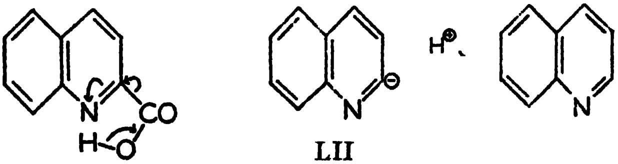
is

$$K_{\text{taut}} = \frac{[A]}{[I]} = \frac{K_a\,(\text{amine})}{K_a\,(\text{imine})} = 10^3$$

The loss in aromatic resonance energy in going from the amine to the imine was 4.5 kcal. per mole. K_a (imine) was estimated by using the K_a of N-methylpyridonimine. From examination of existing evidence these authors concluded that the amino form was also the more stable form for the corresponding amines of quinoline, isoquinoline, acridine, and phenanthridine.

2. Carboxylic acids

The characteristic tendency of α- and γ-carboxylic acids to undergo thermal decarboxylation has been compared with the instability of α-keto acids. The mechanistic studies of Hammick (44, 87) on the decarboxylation of 2-quinolinecarboxylic acid strongly support the following mechanism:



LII

That an intermediate anion (LII) is involved is indicated by the products isolated when carbonyl compounds, quinoline, or m-dinitrobenzene is present during decarboxylation. The long lifetime of this anion is due to the stabilizing effect of the diminished charge density at the alpha position. The stabilization is probably not through resonance delocalization, as the anion is in an sp^2 orbital which is orthogonal to the pi cloud. More likely, it is a direct inductive effect along the sigma bonds toward the nitrogen.

Careful studies on the ease of decarboxylation of α- and γ-carboxylic acids have not been carried out. However, 2,3-pyridinedicarboxylic acid decomposes around 230°C. into nicotinic acid; 2-quinolinecarboxylic acid undergoes decarboxylation above its melting point (158°C.); and 1-isoquinolinecarboxylic acid decomposes at 161°C. Simply heating 6-phenanthridinecarboxylic acid to 150°C. brings about smooth conversion to phenanthridine (223). γ-Carboxylic acids usually require a higher temperature for decarboxylation. 9-Acridinecarboxylic acid yields acridine when heated at 295°C. for a short time (166).

3. Dihydro derivatives

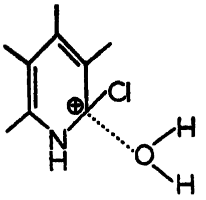
Reduction of heterocyclic bases or the addition of organometallic reagents to the pyridinoid ring leads to dihydro derivatives. As one passes up the series pyridine $<$ quinoline $\simeq$ isoquinoline $<$ acridine $\simeq$ phenanthridine, the stability of the dihydro derivative shows a definite increase. With pyridine it appears that 1,4-dihydro derivatives may be more stable chemically than 1,2-dihydro compounds. The former are the products isolated from the Hantzsch pyridine synthesis (34) and react sluggishly with silver nitrate (202). 1,2-Dihydropyridines are obtained from the alkylation of pyridine with alkyllithium compounds (285) and react readily with silver nitrate (202).

These dihydropyridines together with those of quinoline and isoquinoline are readily oxidized in air and are difficult to isolate in pure condition. On the other hand, acridine (118) and phenanthridine (135) can be converted to fairly stable dihydro products. The increase in the stability of dihydro derivatives of polycyclic systems may be attributed to the decrease in the localization energies of the C=N bond in the parent heterocycle.

4. Halogen derivatives

Halogens situated alpha and gamma to the hetero nitrogen are prone to nucleophilic displacement by such reagents as water, alcohols, phenols, sulfides, and amines (49). Although Chapman and his group (35, 59) have compared halonitrobenzenes with halopyridines by kinetic studies, only qualitative comparisons have been made among halo derivatives of aza-aromatic heterocycles. Bradlow and Vanderwerf (39) studied the hydrolysis of various halopyridines and haloquinolines by heating them with dilute hydrochloric acid. α-Fluoropyridine underwent hydrolysis, whereas the corresponding chloro and bromo derivatives did not. Since 2-chloroquinoline could also be hydrolyzed, it was more reactive than the corresponding pyridine compound. The enhanced reactivity of γ-halopyridines over that of α-halopyridines was attributed to the stability of the tetrahedral transition state (compare Section III,D). By Waters' quinoid hypothesis (268) such a para structure (gamma position) would be more stable than the ortho form (alpha position).

Comparison of the halo derivatives of pyridine, quinoline, isoquinoline, phenanthridine, and acridine shows that the ease of solvolysis increases in the same order. Strikingly enough, 9-chloroacridines and 6-chlorophenanthridines are so prone to solvolysis under neutral or acidic conditions that attempted recrystallization from ethanol leads to extensive conversion to acridones and phenanthridones, respectively. Halo derivatives of diaza- and triaza-aromatic heterocycles show an even greater reactivity. The presence of additional hetero nitrogens further decreases the electron density at the alpha positions (177). Since water and ethanol are nucleophiles of moderate reactivity, it is reasonable to represent the transition state as close to the tetrahedral model (LIII).



LIII

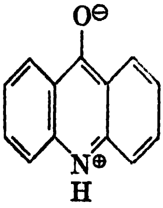
The increased reactivity of halophenanthridines and haloacridines can then be related to the lower localization energies of the alpha and gamma carbon atoms, respectively.

5. Hydroxyl derivatives

The nature of the tautomeric equilibrium for hydroxyl compounds has been given careful study by many workers. 2-Hydroxypyridine can undergo *O*- or *N*-methylation depending upon the conditions. Ultraviolet absorption studies of 2-hydroxypyridine in acidic and basic solutions have been compared with those of *N*-methylpyridone and 2-methoxypyridine, respectively. The resemblance of spectral curves seems to indicate that in neutral or acid solution 2-hydroxypyridine is predominantly in the pyridone form. Similar data were obtained from 4-hydroxypyridine (238).

The 2- and 4-hydroxyquinolines do not show appreciable spectral shifts in solutions of any pH. It was concluded from this that the quinolone tautomer is the more stable form (93). As with the amine-imine tautomeric system, more satisfactory evidence lies in the spectral similarities of carbostyril and *N*-methylquinolone (172).

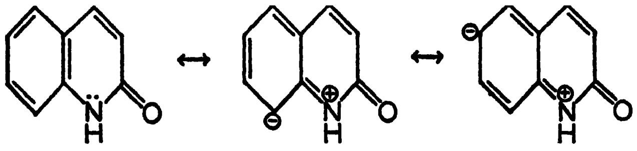
The infrared spectra of acridone and phenanthridone have pronounced carbonyl bands at 6.1 μ and imino bands at 3.1 μ. These compounds therefore seem to be cyclic amides. Moreover, only *N*-methylation has been accomplished. Albert has explained the extreme stability of acridone in terms of "dipolar resonance" contribution (5) (LIV):



LIV

A molecular orbital approach would simply take cognizance of the pi-pi interactions possible between the oxygen and C_9 and the nitrogen and the aromatic pi cloud. Thus, it seems that the ketonic tautomer becomes progressively more stable as one goes from pyridones to acridone (16).

The substitutional chemistry of these derivatives is interesting, since they are prone to electrophilic attack in the benzenoid ring ortho and para to the NH group. This is in accord with a neutral group having unshared electrons adjacent to the benzene ring (137) (LV).

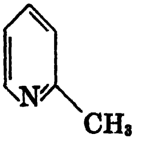


LV

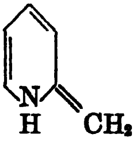
Thus, carbostyril is nitrated in the 6- and 8-positions (105); acridone is sulfonated (122) and nitrated in the 2- and 4-positions (162, 163); and phenanthridone is nitrated in the 2- and 4-positions (57, 203) and brominated, chlorinated, and iodinated in the 2-position (112, 199).

6. Methyl derivatives

Derivatives having methyl groups alpha and gamma to the nitrogen may be considered as methyl ketone ethers in the ammonia analogy of Bergstrom (31). The chemical reactions of such methyl derivatives include halogenation, oxidation, alkylation, and condensation with carbonyl and nitroso reagents (89). The lability of the hydrogen atoms has been explained in terms of a possible tautomeric equilibrium (LVI, LVII).

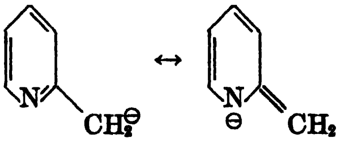


LVI

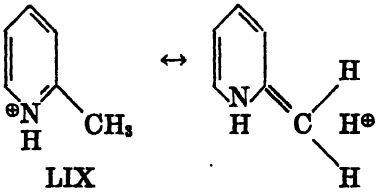


LVII

However, infrared data do not support the presence of much of the imino form (58). Either the anion (LVIII) or the cation (LIX), formed by the abstraction or addition of a proton, respectively, is stabilized by resonance. This stabilization of the charged species should increase both the acidity of the methyl hydrogens and the basicity of the hetero nitrogen.



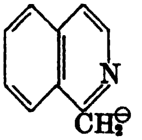
LVIII



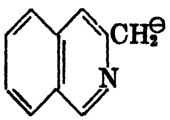
LIX

Hence the behavior of the α- and γ-methyl derivatives is markedly dependent upon the basicity or acidity of the system. As stressed previously, the subsequent chemical reactions will not depend so much upon which tautomer predominates, as upon the electronic demands of the reagent used. Chemical behavior tends to support this interpretation.

In rationalizing the superior reactivity of 1-methylisoquinoline over that of 3-methylisoquinoline Gensler (108) points out that the anion (LX) formed in base-catalyzed condensations has a greater stability due to resonance delocalization than anion LXI.



LX

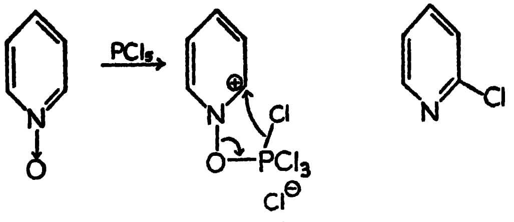


LXI

Consequently, if the base-catalyzed condensations of these methyl compounds with aldehydes depend on the presence of the anion, Gensler's argument could be extended to aza-aromatic heterocycles in general. If one counts the resonance structures stabilizing the anion and assumes that the larger the number, the more stable the anion, one obtains a series of methyl anions of increasing stability. Thus, as one passes up the series 2- and 4-methylpyridines $<$ 2-methylquinoline $\simeq$ 4-methylquinoline $<$ 1-methylisoquinoline $<$ 6-methylphenanthridine $\simeq$ 9-methylacridine, the anion should become increasingly more stable. One would expect both the acidity of the methyl hydrogens and the ease of base-catalyzed condensation to increase in this order.

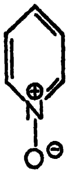
7. *N-Oxides*

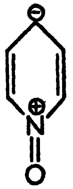
The enhanced reactivity of the alpha and gamma positions in *N*-complexes has already been discussed. The characteristic reaction of *N*-oxides will be considered here. Interactions with such nucleophilic reagents as phosphorus(V) chloride (LXII), potassium cyanide, and Grignard reagents lead to removal of the oxygen and attack at the alpha or gamma position (90).



LXII

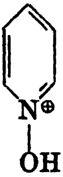
Of great theoretical interest has been the behavior of pyridine-1-oxide with nitric acid. Contrary to expectations this reaction leads to an excellent yield of 4-nitropyridine-1-oxide (204). Both the facility and orientation of this nitration are surprising, as the orientation would suggest a nucleophilic attack by nitric acid. However, a valence-bond description of pyridine-1-oxide shows that the unshared electron pairs on the oxygen can overlap with the pi cloud (LXIII, LXIV).


LXIII


LXIV

Dipole-moment data are in accord with such charge separation (174). Nitration can thus occur electrophilically at the 4-position, which has an enhanced charge density and polarizability.

Recently Mosher and Welch (200) have attempted the sulfonation and bromination of pyridine-1-oxide. Sulfonation occurred at the 3-position and no bromination could be effected. In fuming sulfuric acid the oxygen is probably extensively protonated (LXV),


LXV

and thus the activating influence of the oxygen is diminished. Consequently, orientation would again resemble that of pyridine. Recently, the mercuration of pyridine-1-oxide at the 4-position was reported (254).

The behavior of acridine-10-oxide and phenanthridine-5-oxide toward nucleophilic reagents parallels that of other oxides. Attack occurs at the free gamma or alpha position, respectively.

VI. TABLES OF PHENANTHRIDINE DERIVATIVES

Tables 5 to 11 attempt to include those phenanthridine derivatives reported from 1884 to 1955, with the exception of those previously compiled by Theobald and Schofield (249). It was considered undesirable to list every characterized phenanthridine derivative however, as a multitude of quaternary alkyl halide salts and urethans have been reported. Instead, only the basic derivative is listed and the quaternary salts obtained from it can be found by referring to the accompanying references. If the fundamental system has been characterized only as a quaternary salt derivative, this fact is indicated after the melting point. For example, 8-amino-6-*p*-dimethylaminostyrylphenanthridine has been isolated and analyzed only as its 8-acetylamino 5-methiodide; hence this quaternary salt has been listed as 8-amino-6-*p*-dimethylaminostyrylphenanthridine, m.p. 270–271°C. (8-acetylamino CH_3I).

TABLE 5

Monosubstituted phenanthridine derivatives

Substituent*	Melting Point	References
	°C.	
Phenanthridine....................................	105–106	(205, 247, 248)
1-Amino	115.5–117	(57)
2-Amino	152–153	(57)
3-Amino	144–145	(57)
6-Amino	195.5	(196)
7-Amino	208–210	(57)
8-Amino	203–204	(13, 57)
9-Amino	194–195	(13, 57)
10-Amino	143.5–144.5	(57)
6-*p*-Aminobenzyl	115–120 (CH_3Cl)	(56)
6-*o*-Aminophenyl	168.5	(195)
6-*m*-Aminophenyl	159–161	(195)
6-*p*-Aminophenyl	197–199	(195)
6-[5′,6′-Benzo-2′-(*o*-chlorophenyl)-4′-quinolyl]	260	(182)
6-Benzoyl	152	(223)
6-Benzyl	111–112	(13, 67)
6-Benzylamino	147–148 (sulfonyl)	(99)
6-Benzylaminomethyl	201–203 (HCl)	(99)
2-Bromo	162–163	(111)
6-(5′-Bromo-2′-methoxyphenyl)	148	(182)
6-Phenanthridinebutyric acid	158	(223)
6-Phenanthridine-α-carbethoxyacrylic acid	91 (ethyl ester)	(223)
6-Phenanthridinecarboxaldehyde	141–141.5	(54, 223)
6-Phenanthridinecarboxylic acid	155 (d.)	(223, 256)
6-*o*-Carboxyphenyl	268–270	(147)
6-Chloromethyl	129–131	(99)
6-*o*-Chlorophenyl	125	(182)
6-*m*-Chlorophenyl	137–138	(182)
6-*p*-Chlorophenyl	157.5	(182)
6-Cyanomethyl	105–108	(99)
6-*p*-Cyanostyryl	200–201	(96)
6-Cyclohexenyl	205	(70)
6-(3′,5′-Diaminophenyl)	241 (CH_3Cl)	(258)
6-Diethylaminomethyl	72.5–73	(169)
6-(2′-Diethylaminoethylamino)	238–243 (2HCl)	(256)
6-(4′-Diethylamino-1′-methylbutylamino)	192–193 (dipicrate)	(257)
6-(1′,6′-Dihydro-1′-methyl-6′-oxo-3′-pyridyl)	211–212	(212)
6-(2′,2′-Dihydroxyisopropyl)	129.5	(256)
6-(2′-Diisobutylaminoethylamino)	142–144 (2HCl)	(256)
6-(2′,5′-Dimethoxyphenyl)	163	(182)
6-(3′,4′-Dimethoxyphenyl)	169	(182)
6-Dimethylamino	61.5	(197)
6-(2′-Dimethylaminoethoxymethyl)	190–191 (2HCl)	(99)
6-(2′-Dimethylaminoethyl)	152–154 (HCl)	(99)
6-(2′-Dimethylaminoethylamino)	251–254 (2HCl)	(99)
6-(2′-Dimethylaminoethylaminomethyl)	240 (3HCl)	(99)
6-(*N*,*N*-2′-Dimethylaminoethylbenzylamino)	350–356 (2HCl)	(99)
6-Dimethylaminomethyl	86–87	(169)
6-*p*-Dimethylaminostyryl	236.5–237.5 (CH_3I)	(211)
6-Diphenacylmethyl	157	(223)
2-Ethoxy	95–97	(188)
6-Ethoxy	60	(182)
6-(4′-Ethoxy-3′-methoxyphenyl)	118–120	(182)
6-*p*-Ethoxyphenyl	149–150	(182)
1-Ethyl	233 (picrate)	(151)
2-Ethyl	62–63.5	(151)
3-Ethyl	216 (picrate)	(151)
4-Ethyl	231 (picrate)	(151)
6-Heptyl	50	(70)

TABLE 5—*Concluded*

Substituent*	Melting Point	References
	°C.	
3-Hydroxy	245	(13)
4-Hydroxy	186–188	(33)
8-Hydroxy	281–282	(13)
9-Hydroxy	271–272	(13, 88)
6-(1′-Hydroxy-2′-nitroethyl)	132	(223)
6-*m*-Hydroxyphenyl	225–226	(182)
6-*p*-Hydroxyphenyl	237	(182)
6-*p*-Isopropoxyphenyl	118–119	(182)
6-(4′-Isopropoxy-3′-methoxyphenyl)	137–139	(182)
6-Isopropylaminomethyl	209–210 (2HCl)	(99)
3-Methoxy	57–58	(13)
4-Methoxy	140–142	(33)
8-Methoxy	90	(13)
6-*p*-Methoxybenzyl	125–127	(67)
6-*o*-Methoxyphenyl	127	(182)
6-*m*-Methoxyphenyl	128–129	(182)
6-*p*-Methoxyphenyl	147.5–148	(70, 182)
6-(3′-Methoxy-4′-propoxyphenyl)	128–129	(182)
2-Methyl	89–89.5	(13, 145)
3-Methyl	81	(13, 223)
4-Methyl	95	(145)
6-Methyl	85	(13, 211)
8-Methyl	87.5–88	(13)
6-Methylamino	187	(197)
6-(3′,4′-Methylenedioxyphenyl)	113	(182)
6-(4′-Methyl-1′-piperazylmethyl)	222–223	(9)
6-Methylthio	70–71	(210)
6-*p*-Methylsulfonylphenyl	238	(70)
6-[2′-(4″-Morpholinyl)ethylamino]	258–260 (2HCl)	(99)
6-[2′-(4″-Morpholinyl)ethylaminoethyl]	201–203 (2HCl)	(99)
6-(4′-Morpholinylmethyl)	95	(99, 182)
6-(1′-Naphthyl)	123.5	(214)
1-Nitro	160.5–161.5	(57)
2-Nitro	266–267	(13, 57, 223)
3-Nitro	196–197	(13, 57)
4-Nitro	191–192	(57)
8-Nitro	180	(13, 223)
9-Nitro	194	(13)
10-Nitro	166–166.5	(57)
6-*p*-Nitrobenzyl	168–169	(56)
6-(5′-Nitro-2′-furyl)	187	(182)
6-Nonyl	47.5–48	(70)
6-Phenoxymethyl	142	(223)
6-(2′-Phenyl-4′-quinolyl)	183–184	(182)
6-(1′-Piperidylethylamino)	265–270 (2HCl)	(256)
6-(1′-Piperidylethyl)	173–176 (2HCl)	(99)
6-(1′-Piperidylmethyl)	98–99	(169, 197)
6-*p*-Propoxyphenyl	116–117	(182)
6-(2′-Pyridyl)	133	(70)
6-(4′-Pyridyl)	160	(182)
6-Phenanthridinepyruvic acid	183–184 (ethyl ester)	(168)
6-(2′-Thienyl)	215 (picrate)	(53)
6-*m*-Tolyl	98–99	(182)
6-*p*-Tolyl	108	(115, 182)
6-Tribromomethyl	181–182	(43)
6-(2′,4′,6′-Trinitroanilino)		(194)
6-Phenanthridinevaleric acid	108–115	(223)

* In a few instances the complete name of the compound is given.

TABLE 6

Disubstituted phenanthridine derivatives

Substituent*	Melting Point	References
	°C.	
3-Alloxy-6-methyl	68–69	(190)
8-Amino-6-*p*-aminobenzoyl	217 (CH$_3$Br)	(55)
8-Amino-6-*p*-aminobenzyl	205 (CH$_3$Cl)	(56)
2-Amino-6-*m*-aminophenyl	201	(182)
2-Amino-6-*p*-aminophenyl	233	(197)
3-Amino-6-*p*-aminophenyl	257 (CH$_3$Cl)	(56)
8-Amino-6-*o*-aminophenyl	158 (CH$_3$Cl)	(260)
8-Amino-6-*m*-aminophenyl	240 (CH$_3$I)	(258)
8-Amino-6-*p*-aminophenyl	208–210	(24, 182)
9-Amino-6-*p*-aminophenyl	>300 (CH$_3$Cl)	(56)
2-Aminophenanthridine-6-carboxaldehyde	215	(54)
3-Aminophenanthridine-6-carboxaldehyde	198–199 (urethan)	(54)
7-Aminophenanthridine-6-carboxaldehyde	221–223 (urethan)	(57)
8-Aminophenanthridine-6-carboxaldehyde	234–235	(54)
9-Aminophenanthridine-6-carboxaldehyde	201–203 (urethan)	(57)
2-Aminophenanthridine-6-carboxylic acid	190	(57)
3-Aminophenanthridine-6-carboxylic acid	183	(57)
7-Aminophenanthridine-6-carboxylic acid	105–110 (urethan)	(57)
8-Aminophenanthridine-6-carboxylic acid	202	(57)
9-Aminophenanthridine-6-carboxylic acid	235	(57)
2-Amino-6-*p*-dimethylaminostyryl	267.5–268.5 (2-acetylamino CH$_3$I)	(211)
8-Amino-6-*p*-dimethylaminostyryl	270–271 (8-acetylamino CH$_3$I)	(211)
2-Amino-6-methyl	152	(196)
3-Amino-6-methyl	174–175	(56)
4-Amino-6-methyl	111–112	(240)
6-Amino-2-methyl	170–171	(131)
6-Amino-4-methyl	116–117	(131)
7-Amino-6-methyl	134.5	(56)
8-Amino-6-methyl	232.5–233.5	(211)
9-Amino-6-methyl	196.5	(56)
8-Amino-6-*p*-nitrobenzoyl	280	(55)
8-Amino-6-*p*-nitrobenzyl	246–247	(56)
3-Amino-6-*p*-nitrophenyl	259	(56)
7-Amino-6-*p*-nitrophenyl	180	(56)
8-Amino-6-*o*-nitrophenyl	230	(260)
8-Amino-6-*p*-nitrophenyl	279	(260)
9-Amino-6-*p*-nitrophenyl	260	(56)
10-Amino-6-*p*-nitrophenyl	221–222	(95)
2-Amino-6-phenyl	248	(182)
8-Amino-6-phenyl	168	(182)
10-Amino-6-phenyl	192–193	(95)
2-Amino-6-(2′-phenyl-4′-quinolyl)	228 (2CH$_3$I)	(182)
2-Amino-6-(3′-pyridyl)	165–166	(212)
8-Amino-6-(3′-pyridyl)	227–229	(212)
6-*m*-Aminophenyl-8-hydroxy	275–277 (CH$_3$Cl)	(67)
6-*m*-Aminophenyl-8-methoxy	236–238 (CH$_3$Cl)	(67)
6-*m*-Aminophenyl-2-nitro	185 (urethan)	(261)
6-*m*-Aminophenyl-8-propoxy	206 (CH$_3$Cl)	(67)
6-*p*-Aminobenzyl-8-hydroxy	252 (CH$_3$Cl)	(67)
6-*p*-Aminobenzyl-8-methoxy	241 (CH$_3$Cl)	(67)
6-*p*-Aminophenyl-8-benzyloxy	184 (CH$_3$Cl)	(67)
6-*p*-Aminophenyl-8-butoxy	190 (CH$_3$Cl)	(67)
6-*p*-Aminophenyl-8-ethoxy	225–226 (CH$_3$Cl)	(67)
6-*p*-Aminophenyl-3-hydroxy	297–298 (CH$_3$Cl)	(67)
6-*p*-Aminophenyl-8-hydroxy	269–271 (CH$_3$Cl)	(67)
6-*p*-Aminophenyl-8-isopropoxy	174–175 (CH$_3$Cl)	(67)
6-*p*-Aminophenyl-3-methoxy	235 (CH$_3$Cl)	(67)
6-*p*-Aminophenyl-8-methoxy	253 (CH$_3$Cl)	(67)
6-*p*-Aminophenyl-2-nitro	297	(261, 262)
6-*p*-Aminophenyl-8-propoxy	215 (CH$_3$Cl)	(67)
8-Benzyloxy-6-methyl	208–209	(67)
8-Benzyloxy-6-*p*-nitrophenyl	180	(67)
2-Bromo-6-*p*-bromophenyl	234–235	(24)

TABLE 6—*Concluded*

Substituent*	Melting Point	References
	°*C.*	
2-Bromo-6-(2′-diethylaminoethylamino)	— (2HCl)	(257)
2-Bromo-6-(4′-diethylamino-1′-methylbutylamino)	217–218 (dipicrate)	(257)
2-Bromo-6-methyl	128–129	(24)
8-Butoxy-6-*p*-nitrophenyl	173	(67)
6-Chloro-2-ethoxy	160–162	(188)
6-Chloro-8-methoxy	107	(257)
4-Chloro-6-methyl	113–114	(240)
x-Chloro-6-methyl	91.5–92.5	(182)
6-Chloro-2-nitro	253–254	(203)
6-Chloro-3-nitro	209	(13)
6-Chloro-4-nitro	178–179	(203)
6-Chloro-8-nitro	207–208	(13, 203)
2-Chloro-6-phenyl	141–142	(182)
8-Chloro-6-phenyl	120	(182)
6-*p*-Chlorophenyl-8-hydroxy	244 (CH_3Cl)	(67)
6-*p*-Chlorophenyl-8-methoxy	157–158	(67)
6-*p*-Chlorophenyl-8-nitro	291	(70)
2-Cyano-6-*p*-cyanophenyl	340	(24)
8-Cyano-6-*p*-cyanophenyl	322–323	(24)
2-Cyano-6-methyl	202–203.5	(24)
6-(3′,5′-Diaminophenyl)-8-methoxy	232 (CH_3Cl)	(67)
6-(2′-Diethylaminoethylamino)-3-methoxy	207 (dipicrate)	(257)
4-(2′-Diethylaminoethylamino)-6-methyl	56–57	(240)
6-(1′,6′-Dihydro-1′-methyl-6′-oxo-3′-pyridyl)-2-nitro	304–305	(212)
6-(1′,6′-Dihydro-1′-methyl-6′-oxo-3′-pyridyl)-8-nitro	339–340	(213)
1,4-Dimethyl	76.5	(145)
2,4-Dimethyl	84.5	(145)
3,6-Dimethyl	104.5–105.5	(211)
6,9-Dimethyl	214 (picrate)	(38)
x,*y*-Dimethyl	241 (picrate)	(130)
2-Dimethylamino-6-methyl	146	(197)
6-(3′,5′-Dinitrophenyl)-8-methoxy	252–253	(67)
8-Ethoxy-6-*p*-nitrophenyl	233	(67)
8-Hydroxy-6-*p*-hydroxyphenyl	264 (CH_3Cl)	(67)
8-Hydroxy-3-iodo	235	(13)
3-Hydroxy-6-methyl	325–327	(190)
7-Hydroxy-6-methyl	>300 (HCl)	(56)
8-Hydroxy-6-methyl	298–300	(67)
8-Hydroxy-6-*m*-nitrophenyl	250	(67)
3-Hydroxy-6-*p*-nitrophenyl	330 (CH_3Cl)	(67)
7-Hydroxy-6-*p*-nitrophenyl	262–263	(56)
8-Hydroxy-6-*p*-nitrophenyl	275	(67)
9-Hydroxy-6-*p*-nitrophenyl	280–282	(56)
8-Hydroxy-6-phenyl	263 (CH_3Cl)	(67)
8-Isopropoxy-6-*p*-nitrophenyl	159–160	(67)
8-Methoxy-6-*p*-methoxyphenyl	94	(67)
3-Methoxy-6-methyl	72–73.5	(190)
8-Methoxy-6-methyl	57	(67)
8-Methoxy-6-*p*-nitrobenzyl	142	(67)
3-Methoxy-6-*p*-nitrophenyl	199	(67)
8-Methoxy-6-*m*-nitrophenyl	183–184	(67)
8-Methoxy-6-*p*-nitrophenyl	233–234	(67)
8-Methoxy-6-phenyl	216–217 (CH_3Cl)	(67)
6-*p*-Methoxyphenyl-8-nitro	232–233	(70)
3-Methyl-6-*p*-dimethylaminostyryl	240–240.5 (CH_3Cl)	(211)
6-Methyl-2-nitro	201	(223)
6-Methyl-4-nitro	167–167.5	(240)
6-Methyl-8-nitro	242–243	(203)
8,9-Methylenedioxy	181	(149)
6-*p*-Methylsulfonylphenyl-8-nitro	292	(70)
2-Nitrophenanthridine-6-carboxaldehyde	241–242	(54)
4-Nitrophenanthridine-6-carboxaldehyde	203–204	(57)
2-Nitrophenanthridine-6-carboxylic acid	265–266	(57)
4-Nitrophenanthridine-6-carboxylic acid	170	(57, 240)
2-Nitro-6-phenyl	228–229	(182)
2-Nitro-6-(2′-phenyl-4′-quinolyl)	>295	(182)
8-Nitro-6-(2′-phenyl-4′-quinolyl)	282	(182)
6-*m*-Nitrophenyl-8-propoxy	146	(67)
6-*p*-Nitrophenyl-8-propoxy	169	(67)

* In a few instances the complete name of the compound is given.

TABLE 7

Tri- and polysubstituted phenanthridine derivatives

Substituent*	Melting Point	References
	°C.	
4-Allyl-3-hydroxy-6-methyl	102–103	(190)
8-Amino-6-*p*-aminophenyl-2-bromo	265	(258)
3-Amino-6-*p*-aminophenyl-8-methoxy	>300 (6-acetylamino CH_3Cl)	(261)
6-Amino-2,4-dimethyl	142–143	(131)
6-Amino-3,8-dinitro	321–322	(4)
8-Amino-3-nitro-6-phenyl	227.5	(261)
6-*m*-Aminophenyl-3,8-diamino	221 (CH_3Cl)	(265)
6-*p*-Aminophenyl-3,8-diamino	246	(264)
6-*p*-Aminophenyl-3,8-dichloro	216 (CH_3Cl)	(173)
6-*p*-Aminophenyl-1,10-dimethyl	134	(223)
6-*p*-Aminophenyl-8-methoxy-3-nitro	221–223 (6-acetylamino)	(261)
6-Benzoyl-3,8-diamino	244	(55)
6-Benzyl-3,8-diamino	259 (bisurethan)	(264)
4-Carbomethoxy-8,9-methylenedioxy	149–151	(150)
2-Chloro-6-*p*-chlorophenyl-8-nitro	315	(70)
6-Chloro-3,8-dinitro	225	(4)
6-Cyclohexyl-3,8-diamino	233–234 (bisurethan)	(264)
3,8-Diaminophenanthridine-6-carboxaldehyde	270–275 (bisurethan)	(54)
3,8-Diamino-6-(5′,6′-dihydro-3′-pyranyl)	215–216 (bisurethan)	(264)
3,8-Diamino-6-*p*-methoxyphenyl	190–192 (bisurethan)	(264)
2,8-Diamino-6-methyl		(64)
3,8-Diamino-6-methyl	265.5	(260)
3,8-Diamino-6-(5′-nitro-2′-furyl)	286–288 (bisurethan)	(264)
3,8-Diamino-6-*m*-nitrophenyl	208.5–210.5 (bisurethan)	(265)
3,8-Diamino-6-*p*-nitrophenyl	247 (bisurethan)	(264)
2,8-Diamino-6-phenyl	194	(258)
3,8-Diamino-6-phenyl	198	(258)
3,8-Diamino-6-(3′-pyridyl)	262–264	(213)
3,8-Diamino-6-(2′-thienyl)	229–230 (bisurethan)	(264)
3,8-Dibromo-6-*p*-nitrophenyl	255	(173)
3,8-Dichloro-6-*p*-nitrophenyl	250	(173)
2,8-Dichloro-6-phenyl	193	(102)
3,8-Dicyano-6-phenyl	302	(173)
3,8-Bis(diethylamino)-6-phenyl	255 ($2CH_3I$)	(265)
6-(1′,6′-Dihydro-1′-methyl-6′-oxo-3′-pyridyl)-3,8-dinitro	>360	(213)
6-(2′,2′-Dihydroxyisopropyl)-2,3,8,9-tetramethoxy	214	(223)
1,10-Dimethyl-6-*p*-nitrophenyl	148	(223)
1,10-Dimethyl-6-phenyl	177 (picrate)	(223)
3,8-Dimethyl-6-phenyl	260–262 (CH_3I)	(264)
3,8-Dinitro-6-*m*-nitrophenyl	305–306	(265)
3,8-Dinitro-6-*p*-nitrophenyl	356–358	(265)
3,8-Dinitro-6-(3′-pyridyl)	293–294	(213)
4-Ethyl-8,9-methylenedioxy	142–143	(150)
6-Ethyl-2,3,8,9-tetramethoxy	202	(223)
2,3,8,9-Tetramethoxy	185	(223)
2,3,8,9-Tetramethoxyphenanthridine-6-carboxylic acid	240	(223)
2,3,8,9-Tetramethoxy-6-(4′-chlorobutyl)	223	(244)
3,6,8-Triamino	200	(4)
2,6,8-Trimethyl	123	(102)

* In a few instances the complete name of the compound is given.

VII. PHYSICAL PROPERTIES

A. MOLECULAR DIMENSIONS

As aza-aromatic heterocycles are derived formally from the parent carbocycles by substituting N for CH, the similarity in bond lengths and bond angles is not surprising. The regular hexagonal configuration of benzene is confirmed by studies

TABLE 8

5,6-Dihydrophenanthridine derivatives

Substituent*	Melting Point	References
	°C.	
5,6-Dihydrophenanthridine	123–125	(284)
8-Acetoxy-5,6-dimethyl	110–111	(55)
5-Acetyl-6-methyl-2-nitro	204	(223)
5-Acetyl-2-nitro	181	(223)
5-Acetyl-8-nitro	176	(223)
8-Amino-6-*p*-aminobenzoyl-5-methyl	174–175 (8-urethan)	(55)
2-Amino-6-*p*-aminophenyl-5-methyl	165–170 (bisurethan)	(55)
8-Amino-5,6-dimethyl	172–173 (8-acetylamino)	(55)
5-Benzoyl-6-cyano	140.5–141.5	(283)
6-Benzoyl-3,8-diamino-5-methyl	193–195 (bisurethan)	(55)
6-Benzyl-5-methyl	175–177 (HCl)	(55)
5-Cinnamalacetyl-6-cyano	229–230	(283)
5-Cinnamalcrotyl-6-cyano	234–236	(283)
5-Cinnamoyl-6-cyano	198–199	(283)
6-Cyano-5-methyl	120	(252)
5-(2′-Cyanoethyl)	150–152	(25)
3,8-Diamino-5,6-dimethyl	169–171 (bisurethan)	(55)
3,8-Diamino-6-butoxy-5-methyl-6-phenyl	215–220	(23)
3,8-Diamino-5-methyl-6-phenyl	184–186 (3,8-diacetylamino)	(55)
5-(2′-Diethylaminoethyl)	158–159 (dipicrate)	(135)
5-(2′-Dimethylaminoethyl)	183–184 (dipicrate)	(135)
6,6-Diphenyl	147.5–148	(115)
5-Ethyl	210 (picrate)	(117)
5-Ethyl-6-methyl	148–149	(98)
5-Formyl-9-hydroxy-5,6-dihydrophenanthridine-8,10-dicarboxylic acid	140–141 (diethyl ester)	(88)
9-Hydroxy-5,6-dihydrophenanthridine-8,10-dicarboxylic acid		(88)
8-Hydroxy-6-methyl	182	(55)
8-Methoxy-6-*p*-methoxyphenyl-5-methyl	94	(55)
6-*p*-Methoxybenzyl-5-methyl	168 (HCl)	(55)
5-Methyl	108	(142)
6-Methyl	89	(25, 223)
6-Methyl-5-(2′-diethylaminoethyl)	186–187 (HCl)	(98)
5-Methyl-6-phenyl	102–103	(55)
5-[2′-(4″-Morpholinyl)ethyl]	189–191 (HCl)	(135)
5-Methyl-6-(1′-nitroethyl)	112.5–113.5	(169)
5-Methyl-6-(1′-nitropropyl)	102–103.5	(169)
6-Phenyl-6-*p*-tolyl	143.5–144	(115)
5-(1′-Piperidylethyl)	236–238 (2HCl)	(135)

* In a few instances the complete name of the compound is given.

of the vibration-rotation spectrum (11). Electron-diffraction measurements of bond lengths in benzene gave 1.39 ± 0.02 Å. for C—C and 1.08 ± 0.04 Å. for C—H. Parallel measurements on the pyridine molecule showed the same dimensions for the C—C and C—H bond lengths within experimental error, and gave a value of 1.37 ± 0.03 Å. for the C—N bond length (230). In the light of a recent measurement of the dipole moment of pyridine by microwave spectroscopy, however, De More, Wilcox, and Goldstein (73) suggested the following parameters: C—N = 1.35–1.36 Å.; C—C = 1.39 Å.; C—H = 1.08 Å.; and the angle CNC = 114–117°. Such a narrowed molecule is in better agreement with the data obtained.

TABLE 9

Other hydrogenated phenanthridine derivatives

Substituent	Melting Point	References
	°C.	
Tetrahydro:		
7,8,9,10-Tetrahydro	64	(131, 145)
Tetrahydro	210–212 (picrate)	(40)
6-Amino-7,8,9,10-tetrahydro	165	(131)
6-Amino-2,4-dimethyl-7,8,9,10-tetrahydro	136–137	(131)
6-Amino-2-methyl-7,8,9,10-tetrahydro	169–170	(131)
6-Amino-4-methyl-7,8,9,10-tetrahydro	121–122	(131)
8,9-Dimethoxy-2,3-dimethyl-6-phenyl-1,1a,4,5a-tetrahydro	178–180	(242)
6,9-Dimethyl-7,8,9,10-tetrahydro	78	(38)
2,3-Dimethyl-8,9-methylenedioxy-1,1a,4,5a-tetrahydro	157–158.5	(242)
7-Hydroxy-6-methyl-7,8,9,10-tetrahydro	167	(237)
7-Oxo-6-methyl-7,8,9,10-tetrahydro	118	(237)
Hexahydro:		
5,6,6a,7,8,10a-Hexahydro	104	(40)
2,3-Dimethoxy-8,9-dimethyl-5,6,6a,7,10,10a-hexahydro	240 (HCl)	(243)
9-Methoxy-1,1a,4,5,5a,6-hexahydro	240–242 (HCl)	(280)
9-Methoxy-5-methyl-1,1a,4,5,5a,6-hexahydro	211.5–213	(280)
5-Methyl-8,9-methylenedioxy-1,1a,4,5,5a,6-hexahydro	239–243 (HCl)	(183)
8,9-Methylenedioxy-1,1a,4,5,5a,6-hexahydro	280–282	(183)
Octahydro:		
1,2,3,4,7,8,9,10-Octahydro	37–38	(62)
5,6,6a,7,8,9,10,10a-Octahydro	72	(40)
Octahydro	74	(154)
2,3-Dihydroxy-9-methoxy-1,1a,2,3,4,5,5a,6-octahydro	212–212	(280)
2,3-Dihydroxy-9-methoxy-5-methyl-1,1a,2,3,4,5,5a,6-octahydro	223–225 (HCl)	(280)
8,9-Dimethyl-5,6,6a,7,8,9,10,10a-octahydro	180–181 (HCl)	(243)
6-Methyl-1,2,3,4,7,8,9,10-octahydro	68	(62)
6-Methyl-1,1a,2,3,4,5,5a,6-octahydro	57–58	(98)

The dimensions of other aza-aromatic heterocycles are probably quite similar to those of the parent carbocycles. One may expect a short carbon–nitrogen bond throughout this series of heterocycles, owing to the polar nature of the bond. As in the case of carbocycles, the C—C and C—N bond lengths in these heterocycles should be related to their multiplicity. In the sense of Pauling (208) bond multiplicity is a measure of the "double-bond character" of a carbon–carbon bond. A high bond multiplicity for a carbon–carbon bond means that it is represented more frequently as C═C in the valence-bond structures of the resonance hybrid. Such a bond will be shorter and will tend to resemble an olefinic bond in chemical behavior. Double-bond reactions such as oxidation by osmium tetroxide, ozonization, and argentation (complexation with silver ion) seem to occur at bonds of high multiplicity (16, 148).

B. MOLAR REFRACTION

The polarizability of a molecule depends upon the displacement of electrons by an electric field and is measured by the molar refraction. Early attempts to set up a system of atomic refraction constants and thus to calculate the molar refraction of a compound *a priori* failed with unsaturated systems. Conjugated

TABLE 10

6(5H)-Phenanthridinone derivatives

Substituent*	Melting Point	References
	°C.	
6(5*H*)-Phenanthridinone..............................	293	(52, 247)
1-Amino	319–323	(57)
2-Amino	285 (urethan)	(57)
3-Amino	250 (urethan)	(57)
7-Amino	295 (urethan)	(57)
8-Amino	319–320	(231a)
9-Amino	280 (urethan)	(57)
10-Amino	330–334	(57)
5-Benzyl-2-ethoxy	156–157	(188)
5-Benzyl-1(or 3)-methoxy	152–154	(188)
5-Benzyl-8,9-methylenedioxy	159–161.5	(191)
N,*N'*-Bis[6(5*H*)-phenanthridinone]	>310	(256)
2-Bromo	323–324	(199, 257)
2-Bromo-5-ethyl	116	(117)
2-Bromo-5-methyl	188–189	(125)
5-Carballoxy	93–94	(155)
5-Carbethoxy	143–144	(155)
5-Carbisopropoxy	123	(155)
5-Carbobenzoxy	134	(155)
5-Carbocyclohexoxy	151	(155)
5-Carbomethoxy	127	(155)
5-Carbopropoxy	76	(155)
5-(2'-carboxyethyl)	162–163	(83)
6(5*H*)-Phenanthridinone-1-carboxylic acid	285	(153)
6(5*H*)-Phenanthridinone-4(or 7)-carboxylic acid	299	(66)
2-Chloro-5-methyl	192	(125)
5-(2'-Cyanoethyl)	169–170.5	(25)
5-(2'-Diethylaminoethyl)	193–195 (HCl)	(99)
2,3-Dimethoxy-8,9-dimethyl-6a,7,8,10a-tetrahydro	220	(243)
2,4(or 7,9)-Dimethyl	258	(60)
2,5-Dimethyl	139	(125)
4,5-Dimethyl	141–142	(125)
8,9-Dimethyl-6a,7,8,9,10,10a-hexahydro	220	(243)
8,9-Dimethyl-6a,7,8,9,10,10a-hexahydro-6-thio	160	(243)
2,4-Dimethyl-7,8,9,10-tetrahydro	123	(234)
1,3-Dinitro-5-methyl	281	(126)
5-Ethyl-2-methoxy	138	(117)
5-Ethyl-4-methoxy	117	(117)
5-Ethyl-2-methyl	97	(117)
Hexahydro	176–178	(4)
4-Methyl	240	(184)
5-Methyl-6(5*H*)-phenanthridinone-9-carboxylic acid	162–163 (methyl ester)	(83)
5-Methyl-8,9-methylenedioxy	238	(103, 149)
5-Methyl-2-nitro	249	(126)
5-Methyl-4-nitro	92–93	(126)
2-Methyl-7,8,9,10-tetrahydro	108	(234)
5-Methyl-6-thio	70	(210)
1-Nitro	325–327	(57)
2-Nitro	380–384	(57, 203, 257)
3-Nitro	349	(57)
4-Nitro	265–267	(57, 203, 240)
8-Nitro	329	(13, 57, 203)
10-Nitro	316–318	(57)
5-Phenyl	118–119	(257)
7,8,9,10-Tetrahydro	272	(36, 131, 282)
6a,7,8,10a-Tetrahydro	194–195	(40)
6a,7,8,10a-Tetrahydro-6(5*H*)-phenanthridinone-7-carboxylic acid	216	(40)
6-Thio	281–283	(210, 248)
2,4,5-Trimethyl	194	(60)

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* In a few instances the complete name of the compound is given.

TABLE 11

Miscellaneous di- and triphenanthridinyl derivatives

Derivative	Melting Point	References
	°*C.*	
3-Azo-8-hydroxyphenanthridine	295	(13)
1,2-Di(2′-amino-6′-phenanthridinyl)ethene	>340 (bisurethan)	(54)
1,2-Di(3′-amino-6′-phenanthridinyl)ethene	310 (bisurethan)	(54)
1,2-Di(8′-amino-6′-phenanthridinyl)ethene	278 (bisurethan)	(54)
1,2-Di(9′-amino-6′-phenanthridinyl)ethene	295–300 (bisurethan)	(57)
1,2-Di(2′-nitro-6′-phenanthridinyl)ethene	>360	(54)
1,2-Di(4′-nitro-6′-phenanthridinyl)ethene	>360	(57)
1,4-Di(6′-phenanthridinyl)butane	214	(223)
1,2-Di(6′-phenanthridinyl)ethane	280–282	(99)
1,2-Di(6′-phenanthridinyl)ethanol	191–192	(54)
1,2-Di(6′-phenanthridinyl)ethene	304–305	(54)
N,*N*-Di(6′-phenanthridinyl)amine	160–161 (sulfonyl)	(99)
N,*N*-Di(6′-phenanthridinyl)isopropylamine	203–205	(99)
1,2,3-Tri(6′-phenanthridinyl)propane	264–266	(54)

TABLE 12

Molar refractions of aza-aromatic heterocycles and their exaltations from calculated values

Heterocycle	Molar Refraction (Found)	Molar Refraction (Calculated)	Difference
Pyridine	24.02	25.16	−1.14
Isoquinoline	41.41	40.49	0.92
Quinoline	41.83	40.49	1.34
Acridine	62.34	55.83	6.51

molecules gave experimental values higher than calculations would predict. In the modern view of conjugation these exaltations are understandable, as they imply a greater electronic polarizability. The delocalization of π-electrons in conjugated systems not only lowers the energy of the ground state of the molecule, but decreases the energy of the lower-lying levels of the excited states even more. The net result is a decrease in electronic excitation energy and an increase in polarizability as the conjugated system is extended (compare Section E). This explains why deviations (exaltations) from values obtained by atomic and group refraction constants become more pronounced as one goes to polycyclic systems. This is shown by the aza-aromatic heterocycles in table 12 (14, 48). Instead of the use of empirical refraction constants a modern treatment of condensed aromatic systems has taken account of the high mobility of the π-electrons and the planarity of the ring system. With these calculations the discrepancy between experimental and predicted molar refractions is significantly smaller (table 13) (233). Referring to the aromatic systems in table 13, one can see that the molar refraction, and hence the mean polarizability, of a given heterocycle is less than that of the parent carbocycle. The polarizability of aromatic systems is markedly anisotropic; the electron cloud is more polarizable in the plane of the ring and less so perpendicular to the plane of the ring. In comparison with the parent carbocycle, the main reduction in polarizability of the nitrogen heterocycle occurs in the direction normal to the molecular plane (160). Previous

TABLE 13

Molar refractions of condensed aromatic systems and their exaltations from calculated values (π-electron treatment)

Compound	Molar Refraction (Found)	Molar Refraction (Calculated)	Difference
Benzene	26.2	26.2	0.0
Naphthalene	44.1	43.5	0.6
Anthracene	65.4	62.0	3.4
Phenanthrene	62.3	62.0	0.3
Pyrene	74.0	70.8	3.2
Isoquinoline	41.6	41.5	0.1
Quinoline	41.8	41.5	0.3
Acridine	64.3	60.2	4.1

TABLE 14

Dipole moments of aza-aromatic heterocycles (benzene solution)

Heterocycle	μ (in Debye Units)	Heterocycle	μ (in Debye Units)
Pyridine	2.21	Phenanthridine	1.50
Quinoline	2.14	Acridine	1.95
Isoquinoline	2.53		

workers had concluded that the main reduction in polarizability in going from benzene to pyridine occurred along the dipolar axis (241).

C. DIPOLE MOMENTS

The significance of dipole data in determining charge distribution in pyridine has been pointed out. The experimental determination of the dipole moment of pyridine has given values ranging from 2.2 D to 2.3 D. The dipole moment of pyridine vapor by microwave spectroscopy is 2.15 ± 0.05 D (73). Middleton and Partington (187) have demonstrated that the solvent employed affects the value obtained from determinations run in solution. A carbon disulfide solution yields a value of 2.10 D, whereas a carbon tetrachloride solution gives 2.33 D for the dipole moment of pyridine.

Comparative dipole-moment data for aza-aromatic heterocycles are given in table 14 for determinations run in benzene (28, 107).

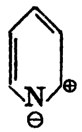
D. INFRARED SPECTRA

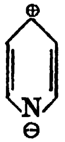
Absorption of photons having a wavelength between 2 μ and 15 μ leads to vibrational excitations in a molecule. These may be stretching or deformation vibrations. Pyridines and quinolines exhibit the following stretching vibrational bands: CH near 3.3 μ; C═C and C═N in the region 6.0–6.3 μ and 6.5 μ. Ring vibrations and CH deformation give bands in the regions 8.4 μ, 9–10 μ, and 11–16 μ. Although the ring vibrations of pyridine closely parallel those of benzene, hydrogen-deformation vibrations are quite different and are shifted to lower frequencies. The C═C and C═N stretching bands are also slightly lower than those of benzene. In quinoline and isoquinoline the region between 6.3 and 6.7 μ has a more complex band structure (26).

E. ULTRAVIOLET SPECTRA

Electromagnetic radiation having a wavelength between 2000 and 7500 Å. embraces the visible and ultraviolet regions. Absorption by a molecule of photons possessing energy in this range may cause promotion of its electrons to higher electronic states. With conjugated molecules not only is the ground-state energy lowered, owing to resonance, but the energy levels of the excited states are sharply lowered. Because of this, the greater the length of a conjugated system the smaller will be the energy difference between the ground state and the lowest-lying excited state. Thus naphthalene shows a bathochromic shift from the maximum in absorption of benzene, as less energetic (longer wavelength) photons are absorbed. As one passes through the series benzene, naphthalene, anthracene, phenanthrene, naphthacene, pentacene, and hexacene, this shift actually brings the absorption into the visible region and a colored molecule results.

From studies made by Mulliken (201) it can be concluded that the greater the increase of polarity of the molecule in the excited state, the greater is the intensity of absorption. As polar forms such as LXVI and LXVII are more important in describing the excited states of pyridine, it is clear why pyridine has an ϵ_{max} of 2000 at 2500 Å., while benzene has an ϵ_{max} of 250 at 2600 Å. In addition, Maccoll (172) has pointed out that in the series benzene, pyridine, pyrimidine, pyridazine, and s-tetrazine the maximum in absorption undergoes a bathochromic shift, the shift being most marked when hetero nitrogens are adjacent.


LXVI


LXVII

In examining the ultraviolet spectra of pyridine, quinoline, isoquinoline, quinazoline, phenanthridine, 5,6-benzoquinoline, and other heterocycles, Badger, Pearce, and Pettit (17) drew these general conclusions. First, there is a considerable loss in fine structure in aza-aromatic heterocycles, but the maxima are not significantly shifted. The absorption shoulders of the nitrogen heterocycles begin, however, at slightly longer wavelengths. Second, the group III maxima between 2500 and 3500 Å. show a uniformly greater intensity in the nitrogen heterocycles.

F. THERMOCHEMICAL DATA

The calculation of resonance energies from the observed heats of combustion or hydrogenation of aromatic compounds and the use of bond energies is a well-known procedure (208). The values obtained for certain carbocycles and heterocycles are given in table 15 (217). The values given show that the resonance energy of a given heterocycle is approximately the same as that of the parent carbocycle. From this it may be judged that isoquinoline and phenanthridine should have resonance energies of around 75 and 120 kcal. per mole, respectively. The large resonance energies of pyridine, quinoline, and acridine indicate that

TABLE 15

Empirical resonance energies of aromatic systems

Compound	Resonance Energy	Compound	Resonance Energy
	kcal./mole		*kcal./mole*
Benzene	41	Pyridine	43
Naphthalene	77	Quinoline	75
Anthracene	116	Acridine	106
Phenanthrene	130	Phenazine	105
Pyrene	152		

no single "static bond" structure can describe the heterocyclic molecule adequately.

VIII. PHYSIOLOGICAL PROPERTIES

Aza-aromatic heterocycles and their derivatives have received much attention from the biological chemist because of their pronounced physiological properties. The alkaloids studied by early workers with natural products were found to contain such ring systems as the pyridine, quinoline, and isoquinoline nuclei. Moreover, the dietary factors nicotinic acid and pyridoxine are now known to be pyridine derivatives. With the advent of chemotherapy many research workers sought to modify the structures of known alkaloids, in order to obtain physiologically active agents which were less toxic. As a natural extension many basic derivatives of aza-aromatic heterocycles were screened for biological activity and with considerable success. The vast amount of research carried out in this quest for chemotherapeutic agents is adequately covered in several reviews (50, 136, 140, 246). Summarily, it might be stated that pyridine derivatives such as cetylpyridinium chloride and 5-amino-2-butoxypyridine are employed as antiseptics; isoquinoline systems are present in narcotics (heroin) and in antispasmodics (papaverine); quinoline and acridine derivatives (Atabrine, Plasmochin) are satisfactory antimalarial agents; and phenanthridine compounds are effective against sleeping sickness in cattle.

In view of the diversified physiological activity of aza-aromatic heterocycles no comprehensive correlation of activity and chemical constitution is to be expected. Recently, however, Albert, Rubbo, and Burvill (8) have made an extensive study of the antibacterial activity of aza-aromatic systems and have proposed that the bacteriostatic action of these bases depends upon ionization and molecular shape. Acridines which were more than 50 per cent ionized (as cations) at 37°C. were found to exert a strong bacteriostatic action. Certain acridines, however, possessed the required degree of cationic ionization but were only feebly antibacterial. These latter compounds all involved "dimensional factors." For example, 9-amino-1,2,3,4-tetrahydroacridine is shown by Hirschfelder models to be nonplanar. Proceeding from Ehrlich's principle (136) that "*Corpora non agunt nisi fixata,*" the authors proposed that the acridine cations are attracted to the anions of nucleoproteins and lie flat on the bacterial surface. The stability of this union is enhanced by the van der Waals forces arising from the large aromatic pi cloud. If the molecule has too small a planar area (pyridines and quinolines) or if it is less planar due to hydrogenation (9-amino-1,2,3,4-tetrahydroacridine), van der Waals forces cannot maintain the drug-protein union. Bulky side chains can inhibit this planar union also. As support for this hypothesis, inactive 2-methylquinolines could be changed into effective bacteriostats by condensing them with benzaldehyde. Presumably the planar styryl side chain enhances the flat area of the molecule and thus increases the secondary forces of attraction. From related experiments the authors concluded that the critical area of the molecular plane should be between 28 and 38 Å.^{2}

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